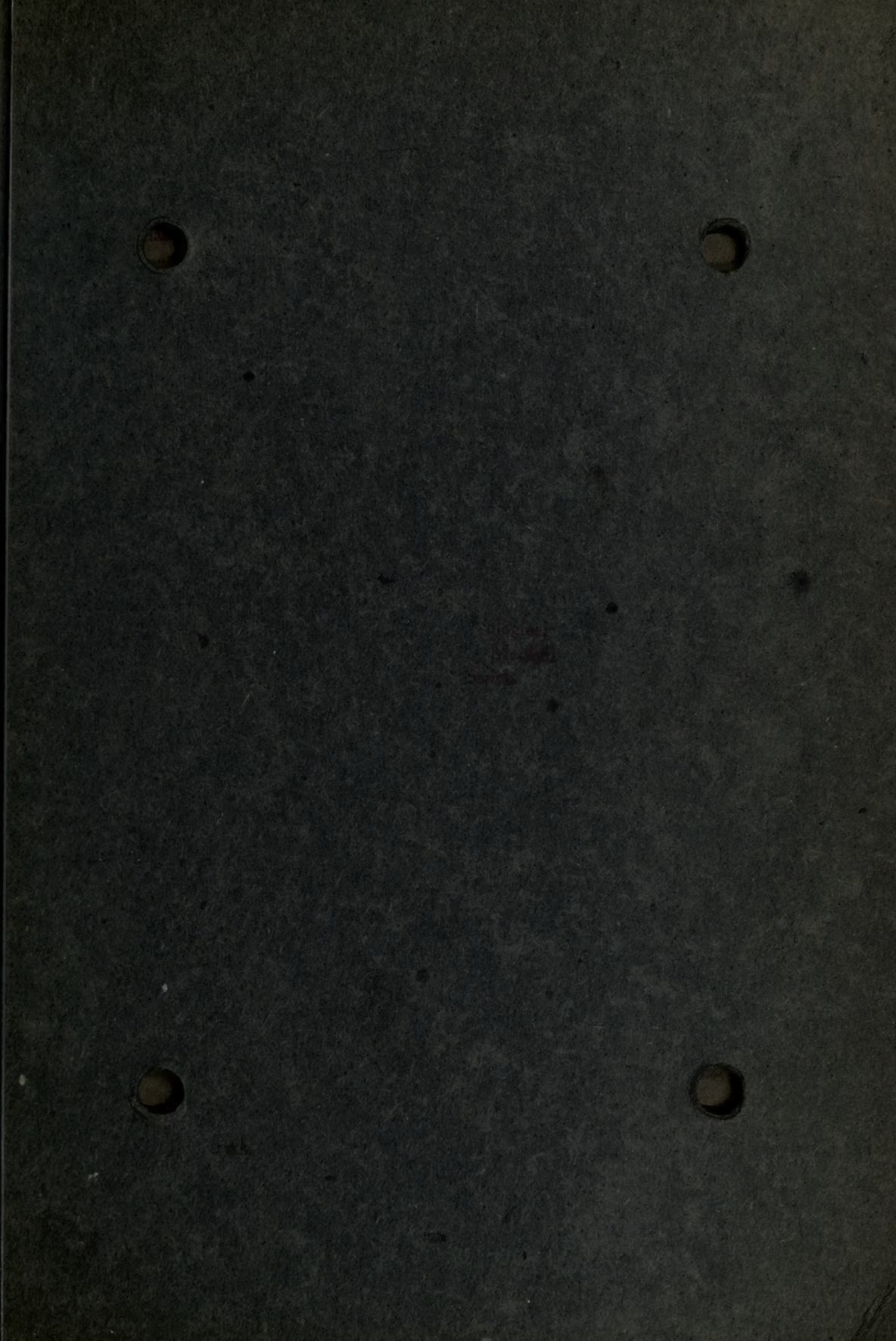
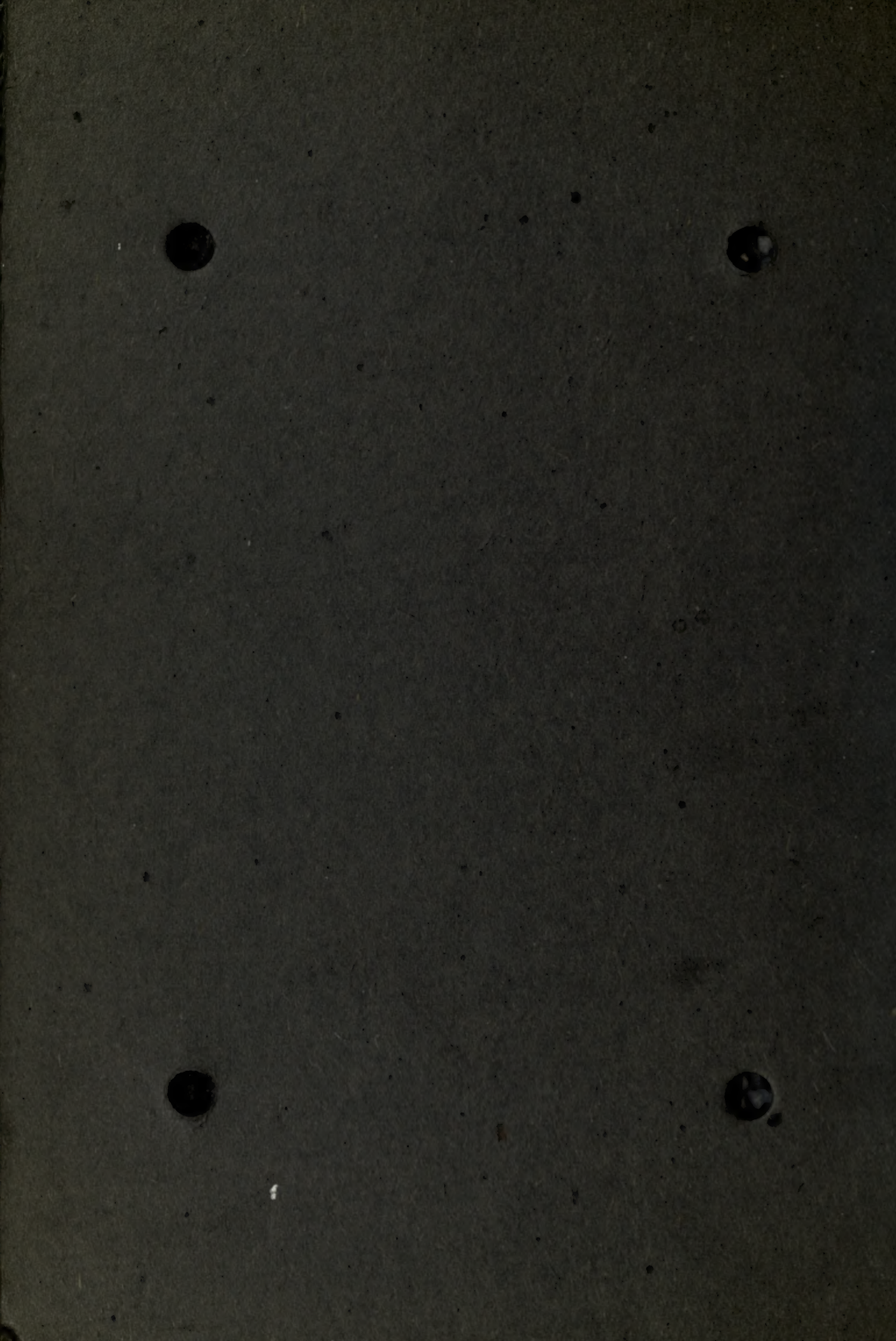






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THE SENSITIVITY OF NORMAL AND DEFECTIVE EARS FOR TONES AT VARIOUS FREQUENCIES

JOHN P. MINTON AND J. GORDON WILSON

January 25, 1921

The anatomic structure and the physiologic action of the ear have proved most difficult to investigate. In the eye, with the ophthalmoscope, one can see into and through the conducting media to the endings of the nerve. It is otherwise in the ear. In the normal ear the drum membrane shuts off the tympanic cavity from observation; with this membrane gone we get a view of the cavity, usually distorted. Under no circumstances can one see the nerve ending in the living. To make examination more difficult, nature has enclosed this nerve ending in extremely hard bone. If one desires to investigate the ending, after removal of the bone from the skull, the dense bone must either be broken or decalcified. If we break the bone, tearing of the soft structures results; if we decalcify, the decalcification with its acids and alcohols inevitably leads to changes in the delicate structure. In spite of these difficulties, we have a fairly accurate anatomic knowledge of the ear, sufficiently clear to indicate that here we have the most complex peripheral end organ with which nature has endowed man. This complexity, together with the analysis of sound it is capable of effecting, has offered a tempting field for speculation as to its mode of action. Yet little has been done in actual physical investigation of the living organ itself.

Within the last decade we have learned to apply to clinical cases, that physiologic knowledge of the vestibular function of the ear which had been growing up for half a century before this time, and as a result we have advanced the diagnosis of peripheral vestibular lesions and thrown some light on obscure central lesions involving the pathway and connections of the vestibular nerve. But in the field of hearing our physiologic knowledge and our clinical application of it are much as Helmholtz left it 50 years ago.

All agree that the ear is a mechanism constructed for at least two purposes: (1) to conduct sound vibration; (2) to perceive simple harmonic waves (simple tones), and to resolve into their component parts (simple harmonic waves) aerial vibrations compounded of different frequencies (itches) which reach the ear together, and in this

analysis to stimulate nerves spread out in a particular linear formation. To what degree this analysis takes place centrally or peripherally does not concern us at present.

There are few subdivisions of medicine in which the specialist is more indebted to and dependent on the physicist than in otology. The middle ear which serves to conduct the sound waves, is designed, as Helmholtz pointed out, to solve the mechanical problem how best to transform a motion of great amplitude and little force such as impinges on the drum, into a motion of small amplitude and great force, such as has to be communicated by the stapes to the fluid in the labyrinth. The second part of the problem, which refers to the means by which the nerve endings are stimulated and the transformation of simple or compound sound vibrations into nerve vibrations, is no less a physical problem, for the internal ear contains at least three structures apparently capable of being set in vibration by sound waves.

In investigating hearing much has been attempted in the past by taking known anatomic structures and endeavoring to endow them with requisite physical properties. In pursuance of this, mechanical models have been built incorporating known anatomic data to show how the ear functions. The results have been stimulating but not satisfying. The attempt is here made to reverse this point of view, namely, to get physical data about audition in normal and defective ears and later to apply these to the normal or pathologic conditions present in the ear examined. The hope is that by a study of such cases we may arrive at a clearer knowledge of the physiologic functions of the various factors which enter into the peripheral mechanism of hearing.

The classical work on hearing was written by a physicist and physiologist—Helmholtz. In 1862, he published his "Sensations of Tone" and propounded his resonant theory of hearing—a theory modified by himself in later editions as new anatomic data were added, a theory which in spite of many objections still influences the work of physiologists and in which the central idea of analysis of sound by resonance has the support of most of them. From the stimulus of that work most of our great aurists of the past drew their inspiration, and on its results they explained many of their clinical findings. That work, Helmholtz tells us, necessitated new instruments of research. We have in the audion oscillator an instrument which far surpasses in its accuracy and delicacy any of its predecessors, and we have tried to harness it to the work.

To test hearing we have methods which enable us to ascertain fairly accurately whether the lesion lies in the conducting mechanism of the middle ear or in the nerve including its endings. This is a wide generalization which has served well in the past, but which leaves much that is important unanswered. Thus, we have no test allowing us to state where in the conducting mechanism the fault lies. Supposing the drum membrane should be indrawn and have its curvature altered, we are not able to say whether the deficiency in hearing is due to this or to some added deficiency of movement of one or more of the ossicles; or if the membrane should be relaxed, we are unable to state how much deficiency of hearing hereby results. Various questions are constantly presenting themselves, to which we can give no satisfactory reply; such as which defaults in hearing are associated with perforations in various quadrants of the drum—quantitatively and qualitatively, or, in combinations of middle ear and nerve deafness, which factor predominates and to what degree. During war service at the front one of us (J. G. W.) noted cases of deficiency of hearing corresponding to what the ophthalmologist calls limitations of the fields of vision—a marked diminution of hearing in which there was absolute deafness at both ends of the scale, the remaining zone of hearing much diminished in acuity corresponding to regions of recognized maximum sensitivity, a condition which might be regarded as due to a general depression of hearing. Until now we have had no method of mapping these out with any degree of accuracy. Then there is the question of “choked labyrinth,” corresponding to choked disk, the importance of which need not be elaborated.

It has long been recognized by physicists that the estimation of the minimum audibility of sound at all pitches is of prime importance in the study of audition. But the range of tones to be examined and the difficulty of obtaining suitable apparatus capable of examining such audibility over so great a range have proved a great barrier. Various methods have been used to estimate the minimum intensity of sound at a given pitch necessary for audibility (the amplitude of just audible sounds). Thus Rayleigh for high notes used a whistle operated by constant air pressure, and tuning forks for low notes. The whistle was mounted on a Wolfe bottle, attached to which was a siphon manometer to regulate a constant air pressure. The distance at which the sound could be heard was ascertained under as far as possible constant atmospheric conditions. One serious objection to these observations was

the distance the observer had to go from the source of the sound—in this case 820 meters—involving the disturbing influence of atmospheric factors. To estimate the minimum audibility of low notes, tuning forks were used which enabled Rayleigh to approximate the sound to the ear. Most of the physical observations of audible sounds and some of our best clinical testings have been made by the use of tuning forks used in various ways. Thus, to test the minimum audibility Gradenigo, an Italian otologist, attached to the upper end of a fork a dark triangle on a white background. When the fork is struck there is a double vision. One sees two pale triangles with a black triangle common to both; the greater the amplitude the greater the space separating the two triangles; as the amplitude diminishes the two triangles merge more and more into the single black triangle. By noticing the extent of the field when the patient ceases to hear (marked by a millimeter scale), one can estimate the hearing power. This method, however, is only applicable to low tones.

The siren, one of the oldest instruments to produce a continuous series of sounds at different pitches, has frequently been used to estimate the minimum audibility of sound. Wien, whose work is quoted freely by German otologists and physicists, used an electric siren conveying the sound to the ear by means of a telephone. He placed the maximum sensitivity of the ear to sound at about 1,200 to 2,000 d. v., from which area the sensitivity dropped off rapidly on both sides. His results, which have been extensively quoted by physiologists and otologists, do not appear to be generally accepted by physicists.¹

Recently at the State University of Iowa, in the otologic and psychologic department, a modification of the electric siren (an audiometer) has been used to estimate the minimum audibility in normal and defective ears. The curves outlined are defective in so far that the instrument has failed to give the minimum audibility at pitches between 1,000 and 2,500 d. v.² Further, no corrections seem to have been made for the vibratory characteristics of the receiver, and with a given strength of current the absolute intensity of sound has not been determined. It is also difficult to see how overtones can be excluded by this instrument. Yet with all these defects, for comparative results it is claimed the instrument has proved valuable for otologic work.

1. Winkelmann: *Handbuch der physik.*, 2, p. 248.

2. *Trans. Amer. Otol. Soc.*, 1920, 15, p. 37.

Not only is the estimation of the minimum audibility of sound at all pitches important for the understanding of audition, but the testing of minimum audibility of various pitches is of importance in otology: (1) To determine the degree of impairment of hearing; (2) to localize the pathologic changes, for ocular examinations may give a negative result in deficiency in hearing, and (3) to estimate the results of our treatment.

The difficulties encountered in testing hearing are considerable. In testing sight we have white light. In testing the ear we have in nature no uniform sound to use as a standard. Both light and sound are vibrations, but the eye is not able and is not called on to resolve light into its composite colors, and even if it were the range of such vibrations is small compared with the ear. In the ear we have a special differentiation of function for such analysis of range.

In estimating hearing, we must have an estimate of the range of hearing (quality of hearing) and the quantitative degree at each pitch. Only with such a record can one have an accurate knowledge of the degree of hearing a patient possesses. Hearing for one part of the scale may be seriously impaired while that of another part is hardly affected. Accurate results can be obtained by estimating quantitatively the hearing for simple tones at all pitches. When one remembers that the qualitative range may be estimated at from 20 d.v. to 20,000 d.v. or higher, one recognizes the wide area to be covered.

At present we depend almost entirely on tuning forks. The overtones in the lower forks are got rid of by clamps and in the higher forks are so much higher that they do not interfere with our present application of the test; we are also aided by the fact that the fundamental tone persists longer than the overtones. Tuning forks, however, have great limitations. They are wanting in scientific accuracy because we cannot well measure the amplitude of their vibration. Each vibration period varies in each set and alters with use. It has been impossible to give a percentage estimate of the impairment of hearing in one ear compared with normal by means of forks, for the amplitude of the tuning fork when it ceases to be heard in the two ears is difficult to estimate.

We have at present no satisfactory means of measuring the intensity of the sound perceived. There is no certainty in regard to the position in the sound scale in which the maximum sensitivity for sound perception lies. Only by observation, such as will be outlined, can we get any such knowledge.

The audition oscillator helps to solve a number of these problems. As will be pointed out, it has shown how similar the curves are in some of our more defined ear lesions. It has shown how a defective mechanical conducting system affects, not a part, but the whole range of hearing. It shows in a surprising way how nerve lesions may differ from lesions in the conducting mechanism—a fact which appears to us to be of fundamental importance in the interpretation of the function of the cochlea. It has thrown interesting light on that most common but most elusive of sensory phenomenon—tinnitus. Above all, the graphic representation of the tone perception in defective ears compared with normal ears affords a startling picture of the degree of loss of hearing.

The accuracy with which the minimum amplitude can be measured is exemplified by testing the same person weeks apart with a minimum of discrepancy, an average deviation of not more than 5 per cent. The application of the oscillator to this problem has not been unattended with difficulty; for instance, the ordinary telephone receiver must be discarded and one constructed of a known natural vibrational frequency—a natural vibrational frequency higher than the pitches we are dealing with. This enables one to get rid of an error which has marred previous published results.

The cases observed by us may be divided into two groups:

1. Those patients who from our present knowledge may be classed as normal, that is, whose ears are positive to our tests for hearing.
2. Those who show deficiency in the hearing tests, including those with and without observable pathologic lesions.

The data presented are limited to an estimation of the minimum audibility of sound at various pitches over a definite part of the auditory scale, from 100 to 5,000 d.v., in normal and diseased ears. We have restricted observation to these ranges because these are the areas most useful to man; they include pitches usually tested and are of sufficient range to detect defects in the conducting and defects in the nerve mechanism as we at present view them.

The question has been raised whether bone conduction interferes with results, for instance, in such a disease as otosclerosis. We have experimental evidence sufficient to answer this in the negative.

In this presentation no attempt will be made to enter debatable territory. We attempt only to state facts as observed by the clinician and facts as obtained by the physicist. It is hoped that by an accumulation of such data trustworthy deductions may be drawn.

METHOD OF TEST

The audion oscillator has been adapted to the purposes of these tests. This oscillator produces a pure sine wave electric current whose frequency or pitch may be varied from 100 to 5,000 or more double vibrations per second. This current is passed through a current adjusting resistance, then through an electric filtering device which takes out any harmonics that might exist, and then through a suitable resistance network into which a special telephone receiver is connected. This receiver is the one used for determining the minimum audibility current at various frequencies for the person who is being tested. A suitable switch is provided to enable the person to listen for intervals of a few seconds, with the tone off between. This insures the reaching of the threshold of audition and completely avoids any fatigue that otherwise might arise.

The results of these tests may be graphically shown in two ways. First, we may plot as a function of frequency the ratio of the current for minimum audibility for an average normal ear to the minimum audibility current for ears being tested, whether they are defective or normal. This gives a graphical picture at all frequencies of the degree of hearing possessed by the patient as compared with the normal ear chosen for reference. Second, we may plot the sensitivity of the ear at various frequencies, when we mean by sensitivity the reciprocal of the minimum vibrational energy for audibility of the special telephone receiver diaphragm at the various frequencies. Both of these methods involve considerable calculations and an accurate knowledge of the characteristics of the telephone receiver. For an understanding and interpretation of the curves it is not necessary to give these details, and they will be omitted for the present.

TESTS OF NORMAL EARS

A number of normal ears, that is, ears without any known physiologic defects, have been tested. Sensitivity curves for two of these ears are shown in Figures 1 and 2. The ordinates of these curves are the reciprocal of the vibrational energy in ergs of the special telephone receiver diaphragm for minimum audibility. The frequency in double vibrations per second is plotted as abscissa. Figure 1 is the curve of a person about 35 years old while Figure 2 is that of a person about 20 years old. The degree of hearing of the former is quite inferior to that of the latter, especially for frequencies above 800

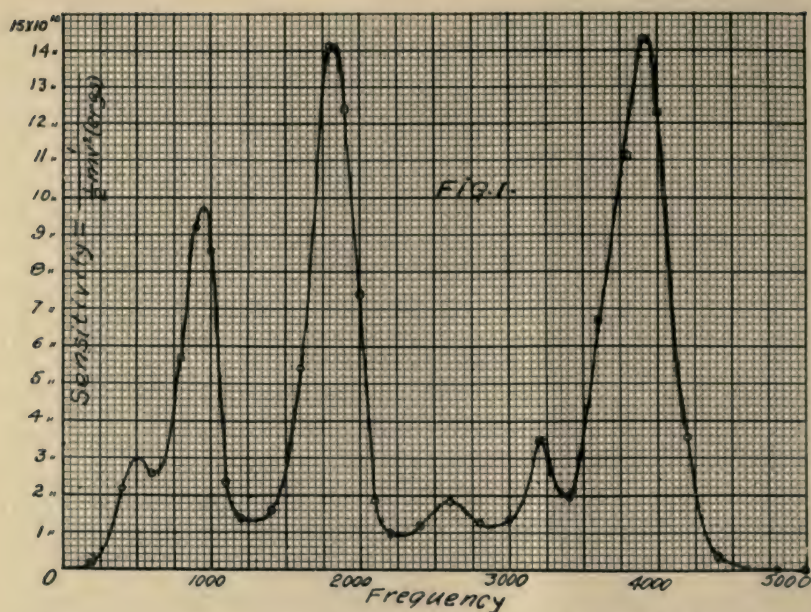


Chart 1.—Sensitivity curve for normal ear of a person 35 years old.

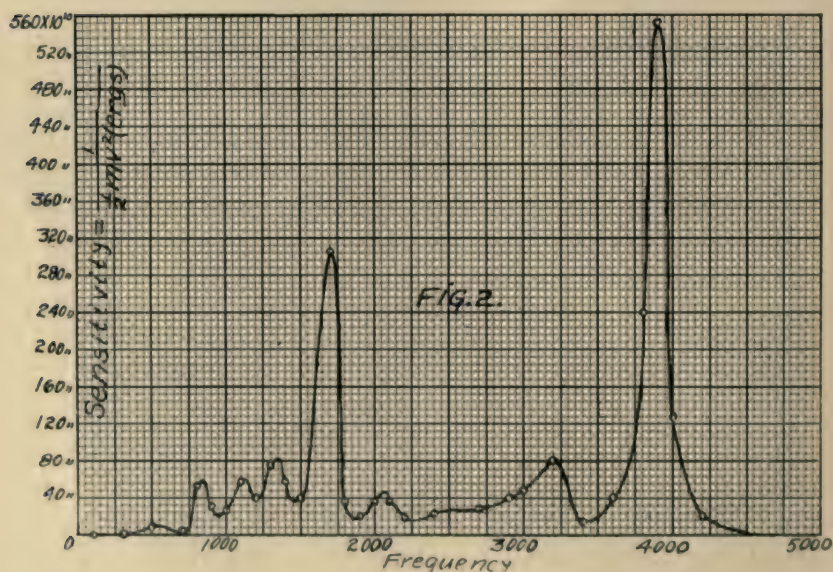


Chart 2.—Sensitivity curve for normal ear of a person 20 years old.

double vibrations. When comparing these two curves, however, one should bear in mind that these curves are in terms of vibrational energy of the special receiver diaphragm whose natural period was 5,215 double vibrations per second. The curves are not in terms of sound intensity or in the degree of loudness as perceived by the ear. Data to be published later will contain these two aspects of hearing.

The most important and interesting things shown by these curves are the large variation in sensitivity at the different frequencies and the existence of such definite maxima of sensitivity. The maxima in the region of 1,800 and 3,900 d.v. are practically in the same location for both ears. These peaks cannot possibly be due to the receiver for its resonant frequency was 5,215 d.v. Moreover, the peaks occurred in practically the same location when the tests were made with the natural period of the receiver in the region of 3,700 d.v. The peaks also occurred in the same region when the cavity formed by the receiver and the auditory canal was almost completely eliminated. Hence, these maxima are not due to the receiver or to the air cavity referred to. Tests with two different oscillators also gave the same maxima. We feel justified, therefore, in drawing the conclusion that these maxima are due to the vibratory characteristics of the mechanical parts of the ear considered as a complex vibratory system.

The well defined maximum at 900 d.v. for Figure 1 is absent for Figure 2. Nevertheless, both curves agree in that the sensitivity begins to increase rather rapidly near 700 d.v. and reaches a peak between 800 and 1,000 d.v. It is also of considerable interest to note that in Figure 1 the peak at 1,800 d.v. is double the frequency of the first maximum and that the peak at 3,900 d.v. is about double the frequency of the one at 1,800 d.v. In a complex coupled mechanical system, which the human ear resembles in many respects, the maxima are not to be thought of as harmonics of the first maximum, but rather as resonant frequencies of the particular coupled system.

Curves are being taken of more normal ears, and when a large number of them have been tested we shall be able to place more reliance on the conclusions than we are able to at the present time.

TESTS OF DEFECTIVE EARS

Tests have been made of numerous ears with various pathologic defects, but the results of these tests will be given for only a few cases.

A more detailed account of the present work from the physical point of view will appear in a later paper to be published in one of the physical journals.

Figures 3, 4, 5 and 6 contain curves for certain types of deafness. These curves show a graphical picture of the relative receiver currents for minimum audibility at various frequencies. If these relative

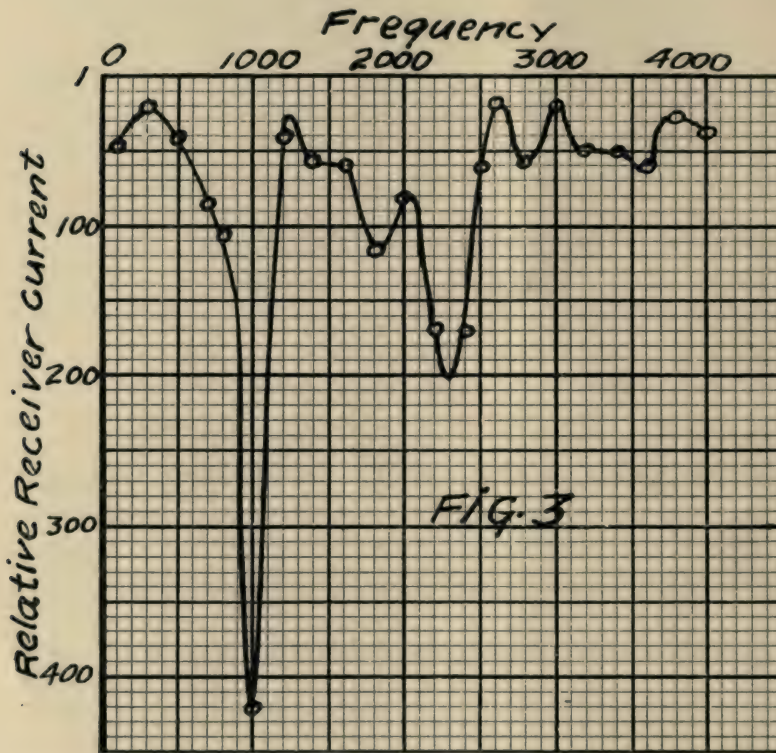


Chart 3.—Curve for left ear of patient, aged 27, with deficiency caused by chronic otitis media since childhood.

receiver currents are squared and then plotted as a function of frequency, the resulting curves will show the relative intensities of the pure tones for minimum audibility of the defective ears compared with the normal. Such curves will give one the correct idea regarding the relative sensitivity that exists among defective and normal ears

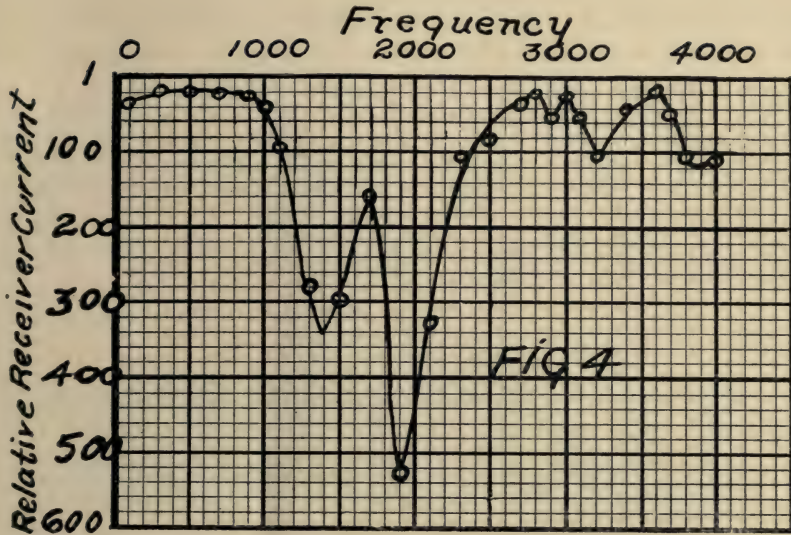


Chart 4.—Curve for right ear of man, aged 42, with bilateral deficiency in hearing.

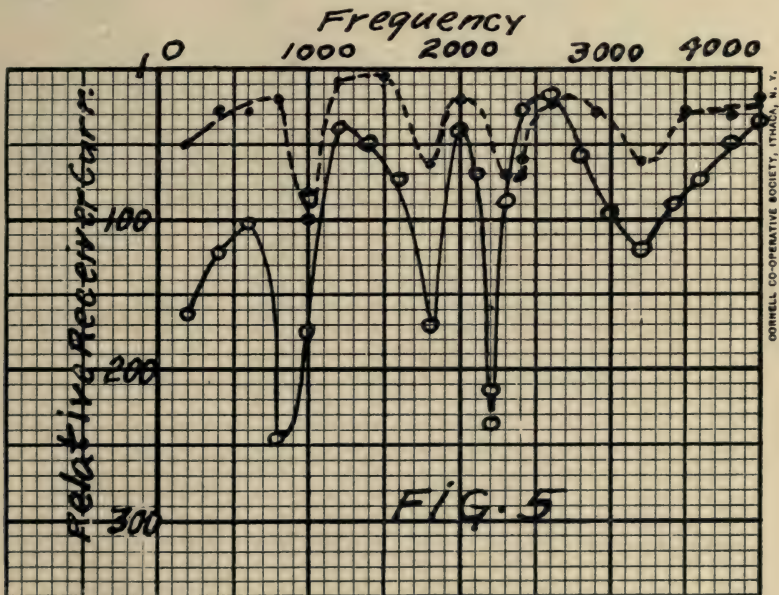


Chart 5.—Curves of hearing of two patients with otosclerosis, upper curve that of girl aged 13, lower curve that of patient aged 34.

at various frequencies. One then begins fully to realize that the normal ear is an extremely sensitive apparatus, possessing a sensitivity of the same order of magnitude as is possessed by the eye.

The curve shown in Figure 3 is that of the left ear of a patient (aged 27) who has had deficient hearing in that ear dating from chronic otitis media in childhood. Tests showed middle ear deafness. The drum was little thickened, but the malleus was attached to the inner wall of the middle ear. Tinnitus was present only occasionally. The whispered voice was heard at 6 inches.

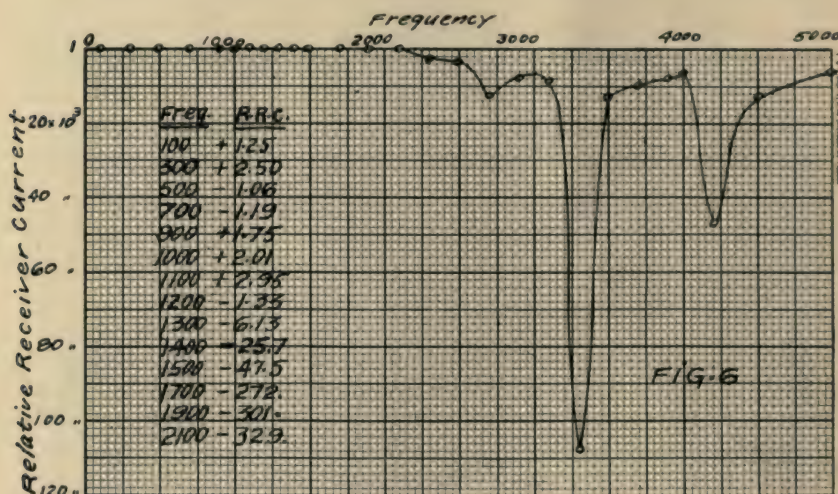


Chart 6.—Curve of hearing of patient 54 years old with nerve deafness.

As shown by the curve, the displacement of the drum membrane and the chain of ossicle bones so far from their natural positions had caused a large depression in hearing, between 800 and 1,200 d.v. which is the most important region for speech sounds. The result was that the hearing of this patient was defective for speech sounds, but for other frequencies the deficiency was not so great. There was considerable depression in sensitivity extending from 1,500 to 2,500 d.v. This curve clearly shows that the pathologic changes in the ear had not caused the same depression at all frequencies. If the curve were plotted to show the sensitivity at various frequencies, as in Figures 1 and 2, one would not find the large increase in sensitivity in the region of 2,000 d.v. that exists in normal ears. This statement also applies to the region of 1,000 d.v.

The curve shown in Figure 4 is for the right ear of a man of 42 years of age whose deficiency in hearing (bilateral) was first noticed 5 years ago. The right ear showed a marked relaxation of the drum membrane in the posterior half. Whispering was heard at 10 inches. The tests showed middle ear deafness, with deficiency in perception of the upper tones. There was no paracusis.

The type of curve for this case is quite different from that shown in Figure 3. There is no depression at 1,000 d.v. (that is, relative to the rest of the curve), but there is a region of a large decrease in the degree of hearing extending from 1,000 to 2,500 d.v. This is the region in which the normal ear has a pronounced maximum; hence, relative to the normal ear there is a marked decrease in this region. It suggests, that the absence of tension throughout the center region of the drum membrane to which the malleus is attached prevents the sound waves from transmitting their energy to the internal ear by means of sympathetic vibrations of the drum membrane and the attached ossicle bones. This indicates that the large increase in sensitivity of normal ears in the region of 2,000 d.v. is due to the resonant characteristics of normal ears.

In Figure 5 are shown two curves of patients suffering from otosclerosis. The upper is that of a girl of 13, with a normal drum membrane, open tubes, bone conduction increased and negative Rinne, with a deficiency in hearing of lower notes and some loss of perception for upper notes. A whisper can be heard $1\frac{1}{2}$ yards; the acumeter at 6 yards. The lower curve is that of a patient, 34 years of age, with deafness of at least 17 years' duration. A whisper could be heard at 8 inches; the acumeter at 2 yards.

The two curves are exactly alike except for magnitude. The upper curve, for the 13-year-old girl, shows that the method of testing gives reliable results for young people. Several curves have been taken for this type of deafness, and the general characteristics are the same for all of them, so long as the disease has been confined to the middle ear. In general, the depression is much larger at the lower frequencies than at the higher ones. There are also the regions of large depressions confined to certain frequency ranges.

In Figure 6 is given the curve of hearing of a patient with nerve deafness. The patient was 54 years old and had noticed bilateral deafness for at least 5 years. Both drums were thickened. The eustachian tubes were open. A whisper was heard at 20 inches and

the acumeter at 8 inches. The Rinne test was positive and bone conduction was diminished. Low notes were heard well but upper notes were not perceived. Slight tinnitus was present but was not troublesome. There was no paracusis.

This curve for so-called nerve deafness shows the surprisingly large variations that exist at the various frequencies. Reference to the data given in the table shows that the relative receiver current up to 1,200 d.v. is on the average about 1, that is, the ear is about normal up to this frequency. Above this frequency the decrease in sensitivity is rapid, especially between 3,100 and 3,500 d.v. This large decrease is of such a nature as to allow the conclusion to be drawn that the disease is not one that has affected a system vibrating as a whole, but one that has affected parts of the ear which are of fundamental importance in audition, and which are loosely coupled to each other and to the rest of the ear. Thus at 3,300 d.v. it requires a vibrational energy which is about 12 billion times greater for the patient to hear than it does for a normal ear to hear, without affecting the region below 1,200 d.v.

A number of curves for nerve deafness have been taken and these data enable us to draw conclusions of importance. It does not seem advisable to attempt at the present time, however, to go into a theoretical discussion of these and other data obtained.

In conclusion, we indicate briefly the theoretical bearing of these data.

1. The existence of the maxima in sensitivity for normal ears shows that they function at the threshold of audition, like an ordinary mechanical system, possessing the same kind of characteristic factors that control such systems.
2. The internal ear functions as though it were laid out in a linear fashion as regards its frequency range, and the data confirm the physiologic teaching that the region of highest frequencies is nearest the stapes and progresses to lower and lower frequencies toward the apex of the cochlea.
3. The internal ear functions not as a single vibrating system, such as a membrane, but as a complex system each member of which is loosely coupled or connected to the rest of the system.
4. There are considerable data at hand to indicate not only that the power of pitch perception lies in the nerve ending, but also that a small group of nerves responds to a small range in frequency. That is, each nerve, including its ending, responds to only one narrow range in frequency and to no other frequencies.

There are other conclusions that we might indicate, but it seems best, as already pointed out, that we should first secure much additional data. However, the statements made seem to show that the present research, of a cooperative nature, when carried further promises to yield results which will throw additional light on many problems connected with hearing both in normal and defective ears.

PHYSICAL FACTORS UNDERLYING THE USE OF RADIUM AND RADIUM EMANATION

GERALD L. WENDT

January 28, 1921

THE RADIATIONS FROM RADIUM SALTS

The complexity of the radiations from an ordinary tube of radium can hardly be overemphasized. The mere division into three classes—alpha, beta, and gamma—is only a preliminary step, for there are present in every such tube at least seven, and usually more, distinct elements, each of which has its own characteristic rays, of one, two, or even all three of these classes, and each of these is incomprehensibly complex. In the clinical use of radium this complexity is often lost sight of, a fact which has hampered the development of radium therapy.

It is well known that these rays arise from the explosions of the radioactive atoms themselves, and that we are here dealing with a source of energy quite different from the usual types. Realization of the amount of this energy is not so common. Radium keeps itself constantly 2 or 3 degrees above the temperature of its environment, due to the absorption of its own rays. The heat thus evolved amounts to about 134 gm. calories per hour from a gram of radium in equilibrium with its decomposition products. Of this, 25 calories come from the radium itself, and 109 from the gaseous emanation and its products. A brief calculation shows that 1 c c of the emanation under these conditions gives no less than 24,300,000 calories before it ceases radiating energy. That this is a stupendous quantity of energy can be shown by comparison with the heat liberated from an ordinary chemical reaction. One c c of mixed hydrogen and oxygen gives, in one of the most energetic of all known chemical reactions, 2 calories. The same quantity of radium emanation gives more than 10,000,000 times this quantity. Obviously the two are not comparable. In the one case we are merely scratching the surface of the atoms. In the other, deep-seated changes take place, and a large fraction of the total energy contained within the atom is made available. Radioactive change of one element into another is a wholly different thing from a chemical reaction. Even the analogy of comparing the chemical heat with the water evaporated from the surface of a watermelon and the radioactive energy to the entire water content of its interior falls far short of the truth.

The Structure of the Atom.—The anatomy of the radium atom needs to be understood before the distinction becomes clear. This was first deduced by Sir Ernest Rutherford, who concluded that almost the entire mass of an atom is concentrated in a dense nucleus at its center. This nucleus theory of the atom has been elaborated mathematically, and has furnished the explanation of so many otherwise unintelligible phenomena that it is now almost universally accepted. According to this theory, the diameter of the nucleus is about 10^{-13} cm. This is only one-hundred-thousandth of the diameter of the hydrogen atom, 10^{-8} , yet practically all the mass of the atom is condensed into this nucleus. The outer part of the atom is composed of rings of electrons in rapid motion, like planets about the sun. To these electrons the chemical properties of the various elements are due, and it is with this exterior that we usually deal. In radioactivity, however, we are only incidentally concerned with the electrons: the rays come from the nucleus. It is only by means of the rays that we obtain any information as to the nature, or even the existence, of the nucleus.

The Alpha Ray Disintegrations.—While the planetary electrons are easily knocked out of the atom, the nucleus is very stable in all atoms except those which for some reason are “radioactive.” In these the nucleus explodes. Of course, each radium atom can explode only once, for what remains cannot be radium; it is, in fact, quite a different substance. Whether any individual radium atom “lives” for a second or for millions of years is a matter of chance. But with the enormous number of atoms in a gram this chance becomes a certainty, and the number of radium atoms which explode per second is strictly proportional to the number present. Of every million radium atoms present at any time, 346 will explode per year, or about 0.00001 per second. With 100 billion radium atoms, one explodes per second. Since there are 10^{21} atoms in a grain of radium, however, such a gram gives 10,000,000,000 such explosions per second. This means that in about 1800 years any quantity of radium will have been reduced to one-half its original amount.

As stated in the foregoing, the energy liberated in these explosions is tremendous. What happens is the ejection from the nucleus of a smaller nucleus, 4 units in atomic weight, at a velocity of 1.6×10^9 cm. or about 10,000 miles per second. All radium explosions emit these particles, the “alpha rays,” which are really nuclei of helium atoms, at this same velocity. On encountering material obstacles they give up

their energy in collisions and are reduced to a velocity such that we can no longer detect them when they have gone through 3.3 cm. of air. Since they all have the same velocity they all go the same distance before they are lost, so that this distance is characteristic and is known as the "range."

What remains of the original radium atom is of course projected in the opposite direction, according to the laws of momentum, at a velocity which is relatively smaller because of the greater weight of the particle, namely, 222 units of atomic weight, radium itself having an atomic weight of 226. These are the "recoil atoms." They are no longer radium. Not only has the nucleus lost 4 units of weight in the explosion, but also, since it is composed of positive electricity and 2 units of positive electricity go off with the helium nucleus, what remains is negatively charged due to the excess of electrons on the outside of the atom. This cannot last, however, and 2 electrons at once drop off. But these are valence electrons, and hence the new atom has a valence 2 less than the radium. Now radium is in the group of the periodic system with barium and has a valence of 2. The new atom therefore has a valence of zero, and is, in fact, a member of the group of noble gases in the periodic system, along with neon, argon, etc. It is called niton, or more usually radium emanation. Why it is a gas rather than a solid is not clear, but it is in every respect a chemically inert gas just like the other gases of that group.

These atoms of the emanation are much less stable than those of radium. One out of every 500,000 explodes per second, and any quantity is thus reduced to half value in a little less than 4 days. Starting with pure radium, there will of course be no alpha rays from the emanation, and during the first minutes after purification the emanation will be so small in quantity that the rays from it will be only a small fraction of those from the radium. As time goes on, however, more and more rays come from the emanation. Take 100 billion radium atoms to start with. One explodes per second. When 500 have thus been converted into emanation the latter will be exploding at the rate of one every thousand seconds. By the time 500,000 atoms of emanation have formed, they will be exploding at the rate of one every second. Hence they are exploding as fast as they are formed. No quantity in excess of these 500,000 can thus be accumulated at any one time from this amount of radium. The two are said to be "in equilibrium." This will occur within a month after all the emanation has been separated from the original radium.

The emanation has a shorter life than the radium. This is accompanied by a greater energy of explosion. Its alpha rays are projected with a velocity of 1.7×10^9 cm. per second and have a range of 4.2 cm. in air. They all have the same velocity and range, but this is different from the range of radium itself. The range of the alpha rays can thus be used as a test to distinguish the two substances. Indeed every radioactive substance that emits alpha rays has its own characteristic range, dependent only on the energy with which it explodes.

The product of the explosion of the emanation atom, called radium A, has an atomic weight of 218 and is again two places to the left in the periodic system. It is thus in the sixth group, since the zero group and the eighth group are chemically the same in this regard. It thus resembles tellurium and has a valence of 6. It also is unstable, even more so than the emanation. One out of every 250 atoms explodes per second, so that it is reduced to half value in 3 minutes. Thus for every 500,000 emanation atoms, and for 100 billion radium atoms only 250 atoms of this radium A can be formed before it decomposes as fast as it is formed. It rapidly reaches equilibrium, and emanation is thus never handled free from it. It can, however, be distinguished by its longer range, which is 4.75 cm.

In a similar way the life periods and ranges of the one further product that gives alpha rays, radium C', can be distinguished. Radium B is an intermediate product which does not give alpha rays on exploding, and will be discussed later. After radium C' comes radium D, whose period is so long and whose activity is therefore so small that it need not be considered.

Thus, every sample of radium in a sealed tube gives out 4 different kinds of alpha rays, corresponding to the 4 different successive products which break up with the emission of the helium nucleus. If the products have reached equilibrium with the radium, as occurs within a month, there will be 4 alpha rays emitted for every radium atom that explodes. Similarly, the emanation separated from radium will reach equilibrium with its products within 3 hours, and will then give 3 alpha rays for each atom of emanation which explodes.

Use of Alpha Rays.—While these explosions in which alpha rays are emitted are the most violent of the radioactive transformations and give about 93% of all the energy that is lost by radiation, this energy can only rarely be used. These rays are effective in producing many chemical reactions, such as the formation of ozone from oxygen, of

hydrochloric acid from hydrogen and chlorine, etc. But for this purpose the radiating substance must be exposed directly to the reacting substances. The walls of an ordinary container would absorb the alpha rays completely. It is possible to use the gaseous emanation in glass tubes so thin that the rays pass through, but the glass may be no thicker than a sheet of tissue paper. If the alpha rays from radium are to be used, the radium must be applied directly or through a very thin coat of varnish. Since the alpha ray of maximum range in air penetrates only 7 cm. of air, and the stopping power of a substance is roughly proportional to its density, and finally, since the density of ordinary materials is about 1,000 times the density of air, it follows that the rays cannot penetrate more than 0.007 cm., or less than 0.1 mm. of any solid or liquid. The penetration is, in fact, only a few hundredths of a millimeter. Only carefully designed "direct applicators" therefore allow the use of these rays.

Furthermore, the rays are of no value except in the treatment of superficial growths, since they cannot penetrate into the tissues. Obviously, as in all chemical reactions, the application of energy to a system has no effect unless that energy is absorbed by the system. A perfectly transparent substance can never be changed by light. So also if the deeper layers have no opportunity to absorb the alpha rays, they can have no effect.

For these reasons we are not concerned as to the possibility of separating the three or four different species of alpha rays from each other. This can be done by interposing very fine screens which absorb the weaker rays and allow the faster ones to pass, but this has no practical purpose.

It is important, however, that the alpha rays can be thus easily absorbed and removed from the more useful beta and gamma rays. Indeed, care should be taken when the latter rays are used that all the alpha rays are absorbed, since they otherwise cause severe surface burns, being about ten times as effective where they do go than are all the other rays together.

The Beta Ray Disintegration.—It has been stated in the foregoing that radium A, which gives alpha rays and is reduced to half value in only 3 minutes, produces radium B. Since the former is in the sixth group of the periodic system, the latter is in the fourth group, being analogous to lead, though it has an atomic weight of 214. This substance is also unstable. Its explosions, however, are of quite a different

nature from those of the elements we have heretofore considered. It explodes rapidly, so that it is reduced to half value in slightly less than half an hour. It does not emit alpha rays, however. All the characteristics of the previous elements are missing. In their stead we observe the emission of rays that are much more penetrating, but which have individually much less energy than have the alpha rays. It has been shown that instead of being positively charged, they are negative, and instead of being of atomic size they are several thousand times smaller. They are, in fact, electrons, and are identical with the atoms of electricity which constitute an electric current when they flow through a wire or through an air gap.

These electrons differ from all other known electrons in their tremendous velocity. Some of them are ejected from the atoms of radium B at a velocity which is 99.8% of the velocity of light; that is, more than 180,000 miles per second. To give an electron such a velocity in air requires a potential of several hundred thousand or even million volts. This fact alone indicates that these electrons, or beta rays, do not come from the surface of the atom, but from its nucleus, where the forces are condensed and sufficiently intense to account for these high velocities.

While the amount of energy carried by each one of these beta rays is less than 1% of the energy of the much larger alpha particle, its velocity is so high that it penetrates considerable thicknesses of matter. They can be detected after passage through as much as a meter of air. They pass through as much as 3 cm. of aluminum. This is due to their velocity and their small size, which allows them to pass through the majority of atoms without encountering material resistance. As stated, the aggregate space occupied by an atom is probably less filled with matter than is the space occupied by the solar system. Like meteors in the astronomical analogy, they can therefore pass through what we consider solid matter with relatively few collisions.

The Gamma Rays.—The emission of beta rays is invariably accompanied by the emission of gamma rays. These latter are radiations in the true sense, i. e., they are not material particles, as are the first two classes mentioned, but are ether waves, similar to light and roentgen-rays. They are distinguished from roentgen rays only by being much shorter in wave-length. Visible light waves are between 0.0007 and 0.0004 cm. in length, or in the more usual units, between 7,000 and 4,000 Angström units. As the wave-length of light decreases all matter

becomes more opaque to it until at about 1,300 A. U. all solids are entirely opaque. Much shorter wave-lengths, however, again penetrate, and when we reach a length of only 1 A. U. we have roentgen rays with their extremely great penetration. The shorter the wave-length the more penetrating a roentgen ray is. Hence the gamma rays, which are in fact roentgen rays with a wave-length of about 0.1 A. U., are the most penetrating of all known rays.

They are generated in the radium just as roentgen rays are generated in a tube. In the latter case a stream of electrons is projected through an evacuated space under a high potential, and thus strikes the material of the anticathode or target at a high velocity. The energy of the collision is radiated largely in the form of short-wave radiation or roentgen rays. The intensity of the roentgen-ray emission depends only on the number of electrons passing, i. e., on the milliamperage. The wave-length of the roentgen rays, however, depends on the velocity of the electrons, i. e., on the potential or the spark-gap. The higher the potential the greater the frequency and the less the wave-length of the roentgen rays. It is, of course, well known that increase of potential gives "harder," i. e., more penetrating and thus shorter wave-length roentgen rays. The conditions within the radium tube are the same. Atoms of radium B and of radium C are constantly exploding and sending out the electrons in the form of beta rays. These collide with the atoms of the various types of radioactive elements present in the tube, and the energy of the collision is similarly radiated in very short waves. But since the energy with which the electron is sent out is much higher than from any potential obtainable in a roentgen-ray tube, the rays thus generated have a correspondingly shorter wave-length. The extremely penetrating gamma rays from radium B correspond to a potential of 200,000 volts, and presumably it is an intra-atomic field of about this strength that projects the beta ray electron.

The beta rays from radium B fall into about 30 different groups of velocities, and thus there are also many groups of wave-lengths in the gamma ray spectrum of this substance. In addition, radium C is present in every radium tube and contributes its own types of gamma rays. Finally, since the velocities of the beta rays are continuously reduced before they finally emerge from the tube, there is also a general distribution of gamma ray wave-lengths, a continuous spectrum.

While the potentials within the radioactive atoms are higher than those conveniently attainable in roentgen-ray work and the gamma

rays are thus more penetrating than roentgen-rays, the intensities of the latter can be made much greater than those of gamma rays. The intensity of such radiation is proportional to the number of electron collisions, and thus can be increased at will to very high values in roentgen-ray tubes, while any one radium tube gives a constant intensity dependent only on the amount of radium B and C it contains.

The Use of Beta and Gamma Rays.—Both these rays may be used in therapy, but the beta rays can never be used without the gamma. Since the latter are so much more penetrating, they cannot be separated from the beta rays by fractional absorption, and since they are light waves they cannot be deflected or removed by other means. Beta ray treatments must therefore count on the presence of the more penetrating though less powerful gamma rays. The energy of the gamma rays is only about 1% of that of the beta rays. For beta ray treatment the radium tube must be used almost bare, i. e., it must not be inclosed in lead. Three to four millimeters of lead will completely absorb the beta rays. A bare tube will give a beta ray penetration of about 2 to 3 cm. in tissue.

This penetration is so low that the gamma rays are much more useful. For effective use without danger of surface burns the tube is covered with a layer of lead to absorb the beta rays. Since gamma rays are more penetrating than roentgen rays, the question of their effective range is only one of intensity. Their energy per square centimeter of course decreases with the square of the distance from the tube, as with all other radiations, and hence to reach deep regions it is often necessary to use "cross fire" methods such that the spot aimed at received repeated doses from various angles, while surrounding tissues are radiated only once from some one of the points of application. When a tube is inserted in a body cavity and the rays are to be used in one direction only, the back of the tube must be covered with heavier lead to prevent the escape of intense radiation. While even a centimeter of lead does not absorb the gamma rays completely, their intensity may thus be cut down to a point below that of effective dosage.

The ability to apply the tube directly to the surface of the lesion in this manner is of course one of the advantages of radium therapy. Because of the inverse square of the distance law, however, in such usage the intensity and therefore the effectiveness of the rays dies off rapidly. When the tube is at some distance from the lesion this is not

true, and a uniform dose may be given to a large area. It should be noted that this law of decrease holds only for light radiations and is not exactly applicable to the material rays like the beta.

One more point should be mentioned. There is a close relation between the electrons which cause roentgen and gamma rays and beta rays. The reverse process is equally common. Thus the passage of either roentgen or gamma rays through matter liberates large numbers of electrons. In the case of the very high frequency gamma rays these liberated electrons themselves attain high velocities, and are, in fact, powerful beta rays. This is also true of the roentgen rays, although the frequency of the ray is less and the velocity of the liberated electron is also less. Furthermore, the roentgen-ray tube is commonly at some distance from the point under treatment, so that these secondary electrons are dissipated. With a radium tube, however, they may be liberated at the very surface of the lead covering which excludes the primary beta rays, and may thus cause a surface burn in spite of heavy lead protection. For this reason the lead tube should be placed within a thin rubber tube. This will absorb the secondary beta rays from the lead, and will itself emit very few electrons under the action of the gamma rays.

The chemical and therefore the therapeutic action of the beta and gamma rays is much the same, and they may be used interchangeably when their penetration and energy are borne in mind. It will be noted that the beta and gamma rays are evolved exclusively by radium B and radium C and not by the radium itself. These beta radiators are themselves products of the radium emanation, a fact which has led to the wide use of the emanation itself in place of radium tubes.

THE USE OF RADIUM EMANATION

It has been pointed out that the alpha rays, while they are the most powerful, are practically useless because of their extremely low penetration, and that for therapeutic purposes only the gamma rays are useful. Hence it is obvious that the radium itself is of no therapeutic use, except as it furnishes radium B and C, for the gamma rays come only from these two elements. Since the only function of the radium is to produce radium B and radium C, it would be advantageous to keep the radium in a secure place and to extract from it these active elements.

This can readily be done by employing the physical properties of the radium emanation. As has been stated, this is a gas analogous in

every way to the gases of the zero group of the periodic system, such as neon and argon. Because of this fact it can easily be separated from radium. Solid radium salts lose their emanation constantly and slowly, but not completely. In order to drive the emanation entirely from a radium salt, the latter must be heated to a high temperature. When, however, a radium salt is dissolved in water, the emanation collects in the water and above it, and it may readily be pumped out and sealed into containers for use.

During the conversion of radium into the emanation only alpha rays are emitted. The gamma rays are thus still to come in subsequent changes, and if the emanation is sealed into small tubes it will there disintegrate to give radium A, B and C, and the tube will thus rapidly become a source of gamma rays.

The Quantity of Emanation Produced.—It has been stated that of every 100 billion radium atoms one explodes per second, and that of every 500,000 emanation atoms one explodes per second. Hence when the original 100 billion radium atoms have produced 500,000 emanation atoms, the latter are exploding as fast as they are formed—one per second—and this quantity of radium can never accumulate a greater quantity of emanation. These 500,000 will of course not be the first 500,000, since these will constantly have been disintegrating. At first the accumulation of emanation will be relatively rapid, since the few then present will be slow in disintegrating. But as the figure of 500,000 is approached, the speeds of formation and of disintegration become more and more equal, so that near the end of the period the effective accumulation of the emanation is very slow. About one-sixth of the final “equilibrium” quantity is accumulated in the first day, and about one-half by the fourth day. At the end of a month the equilibrium is complete.

The quantity of emanation thus accumulated by one gram of radium at equilibrium is known as one curie, and occupies a volume of 0.0006 c.cm. Similarly, a milligram accumulates during a month one millicurie. Thus also each milligram produces 0.16 millicurie during the first day and 0.5 millicurie during the first 4 days after the emanation has been removed. A quantity of 100 mg. therefore produces 16 millicuries in one day, about 50 in 4 days, and 100 in 30 days.

According to this law of accumulation, it is advantageous to pump off the emanation as often as once a day. For example, if 100 mg. of radium are at hand, 16 millicuries may be removed after one day's

accumulation. After another day 16 more will be available, but the first will have decayed to a value of about 13; thus the two together have a value of 29. This total value must be the same as the quantity which would have been obtained from the solution at the end of the second day with no extraction of the first day. The advantage of daily pumping, however, is that, while the total quantity is the same, one whole day's use was obtained from the 16 millicuries pumped the first day.

Tabulating thus the quantities furnished by 100 mg. in solution throughout a week, the advantage of this method is obvious.

TABLE I
VALUE EACH DAY

Sun.	Mon.	Tues.	Wed.	Thurs.	Fri.	Sat.	Sun.	Mon.
16	13	11	9	8	6.5	5.5	4.5	4
	16	13	11	9	8	6.5	5.5	4.5
		16	13	11	9	8	6.5	5.5
			16	13	11	9	8	6.5
				16	13	11	9	8
					16	13	11	9
						16	13	11
							16	13
								16
16	29	40	49	57	63.5	69	73.5	77.5

The total quantities represented by the combined activities of all tubes on hand on any day represent the amount of emanation which could have been extracted on that day if none had been taken from the radium in the interval. Thus, after a day about one-sixth is available; after 4 days, one-half; after a week about three-fourths; after 2 weeks, about 90%, and after a month practically the entire equilibrium quantity of 100 millicuries. The figures are only approximate, and do not allow for the inevitable loss of about 5% in the process of extraction.

After a week each tube has decreased to about one-fourth of its original activity, and in the cases cited is too weak to be of much therapeutic value. Several such tubes are then conveniently mounted together in a frame or on a strip of tape to give an applicator of their combined value but distributed over a greater area. Or they can, with proper apparatus, be opened and their combined contents can be introduced again into a single tube with practically no loss. In the continuous use of the emanation extraction apparatus with daily removal of the gas, 92 to 96 millicuries would at all times be available, distributed in tubes of various strengths as indicated. In the case of larger quanti-

ties of radium the quantities of emanation would of course be proportionately increased.

In order to follow the extraction work accurately and to insure proper dosage in treatments, it is extremely desirable to have at hand one of the various types of measuring instruments. Instruments have been devised which will show on a scale reading directly in millicuries the value of each tube by simply placing it in a receiver at the proper position of the instrument. Such instruments can be conveniently used by nurses and others not skilled in radioactive measurements.

Convenience and Applications of the Emanation Tubes.—The chief argument for the use of the emanation rather than the radium itself is the insurance against loss of the radium. The latter is kept securely locked in a safe, and is at no time in serious danger of loss. In practice radium tubes are frequently removed with bandages, or work their way loose, or are misplaced. If this happens in the case of an emanation tube, there is no real loss, since the tubes have no intrinsic value and would decay to worthlessness in a few days in any case. Thus the entire gamma ray activity of the radium is at all times available, with no risk whatever.

There are, however, other arguments in favor of the use of the emanation. It can be concentrated into extremely small volume. Sixteen millicuries of emanation can be put into a tube with a total diameter of 0.5 mm. and a length of 5 mm., which is far less than the size of a capsule containing 16 mg., the corresponding quantity, of radium salt. This is often a critical factor in their application. An emanation tube can, for instance, easily be introduced into a trochar and inserted into body cavities by puncturing or otherwise when a similar procedure in case of the large radium tube would be out of the question. Greater flexibility is also possible, since the tubes can be made of any size or shape and, furthermore, can be arranged in applicators of any desired strength by combining tubes of various strengths either in one tube or by distributing them over any desired area.

There are several precautions which have not yet been mentioned. One is that the gamma rays do not come from the emanation itself, but from the products of its disintegration; i. e., from radium B and C. Hence when the emanation is first introduced into the glass tubes it is free from these products and gives no beta or gamma rays. These rapidly develop, however, and in the course of 3 hours radium A and B have reached their equilibrium quantity so that the tube is at its full

gamma ray strength. Another necessary precaution is the enclosure of the extremely fragile tiny glass tubes within steel needles or other protective covering when in use. Such a needle need not exceed a millimeter in diameter, even for 50 millicuries of emanation.

Other Applications.—The emanation extraction apparatus allows still further variations. In case of surface treatments it may become desirable to make a direct application of a strongly radioactive preparation which makes use of the alpha and beta rays. For this purpose sheets of silver or of copper may be inclosed in a glass vessel and allowed to stand in contact with the emanation for several hours. They will thus take up a deposit of radium A, B, and C, which serves as an extremely active source of radiation while these elements last, which is about three hours. Very fine needles may thus be activated for work in confined areas.

Furthermore, radioactive preparations for intravenous or other injections may be prepared by similarly exposing sodium chloride to the emanation and allowing it to take up these active elements. The solution of the salt for injection is then temporarily strongly radioactive. Such solutions are not subject to the objections that apply to the injection of radium itself, for the question of their elimination by the system is not involved. In the course of three hours their activity dies out almost completely, and if longer treatments are desired the injections must be repeated.

Finally, in the case of massive tumors it is occasionally desirable to give a prolonged treatment. This can be done by inserting or burying the emanation tube within the mass of the tumor and allowing it to remain until its activity is lost or until the tumor is removed.

HISTOCHEMICAL STUDIES ON THE MECHANISM OF RENAL SECRETION

EDWARD J. STIEGLITZ

From the Department of Anatomy, University of Chicago

February 25, 1921

The multitude of views concerning the true mechanism of renal function falls into two categories of general, conflicting opinions or schools. The one, first suggested by Ludwig, assumed the glomerulus to be the seat of chief activity, and the urine to be a filtrate from that organ. To this Cushny has added the idea of reabsorptive activity by the convoluted tubules, thereby explaining the concentration of the urine and the retention of threshold bodies, such as sodium chloride. The other view, bearing the joint names of Bowman and Heidenhain, lays stress on the process of secretion of solutes by the convoluted tubules, these structures thus raising the concentration of the urine.

The problem which presents itself, therefore, in its simplest form is the determination of the direction of progress of the electrolytic urinary components as they pass through the cells of the convoluted tubules. To study this progress with electrolytic salts rather than with colloidal dyes, as has been done heretofore, is desirable because salts are substance normally secreted into the urine, while the dyes are obviously foreign. In our experiments iron was chosen for the work because: 1. It is normally secreted. 2. It is very readily detected in minute quantities by the Prussian blue reaction. 3. There is no free (detectable) iron normally in renal tissue. 4. It forms nontoxic salts. The green ferric ammonium citrate was found most satisfactory, the more commonly known red salt being much more toxic because of an unsaturated carboxyl group.

In studying the mechanism of iron elimination by the kidney, two questions are to be considered: 1. What is the route of the iron in its passage? 2. What does the iron do to the kidney? Series of experiments were carried out along the following lines: Large doses of ferric ammonium citrate were injected intravenously into rabbits and the animals killed at various intervals following the injection; the kidneys were at once fixed in 95% alcohol and paraffin sections prepared and

the Prussian blue precipitated by treatment of the sections with sodium ferrocyanide in dilute acid solution. The time ranged from 0.5 minute to several days. A series of such preparations at 0.5, 1, 2, 3, 5, 7, 10, 12, 15, and 20 minutes and more showed the direction of movement of the iron through the convoluted tubules as the multiple exposures of a cinema reveal motion. The fine blue particulate granules of Prussian blue first appeared at the basal pole of the cells at 1 to 3 minutes. After from 3 to 5 minutes it had progressed to the level of the nuclei and after 5 to 7 minutes it reached the free border and entered the lumen. After that time the greatest intracellular concentration of iron was always just under the brush border at the lumen. In the several hundred sections studied iron was never seen in the spaces of the glomerular capsule. This series adds further evidence to the conception of a secretory function of the convoluted tubules.

Not all the iron reaching the kidney is eliminated, however. The urine becomes negative for iron in about 5 hours, but long after that, for several days in fact, there is iron in the convoluted tubule cells. It is practically all just under the brush border, indicating a marked cellular polarity. Furthermore, this retention of iron is accumulative if the animal is given multiple injections over a period of weeks, and this accumulative retention has distinct effects on renal function: 1. There is a constantly increasing period of elimination of the iron with each further administration, the secretion being slowed by the block. 2. There is a decrease in the quantity of iron eliminated with each new injection. 3. There is a marked fall in the ability to secrete phenolsulphonephthalein after several injections of iron.

The effect of the iron on the renal processes was the most interesting phase of the subject. 1. Iron does not appear in the bladder urine before 10 minutes after injection. 2. Its concentration rises quickly and falls slowly until after about 5 hours there is no more iron. 3. There is at first a brief transient diuresis, and then, during the height of iron elimination there is a marked fall in the water excretion, which only rises again as the iron disappears. We found this fall entirely unassociated with blood pressure or temperature changes. Furthermore, during the elimination of iron there always was: (1) a marked fall in the specific gravity of the urine, e. g., from 1.020 to 1.008; (2) a disappearance of carbonates from the urine. (Rabbit urine is normally cloudy with carbonates, but during the time iron was

being passed there were none. The urine remained alkaline, the iron being in the form of dark brown ferric hydroxide.)

The explanation of these effects on renal mechanics is correlated with Martin Fischer's views on the mechanism of edema. Ferric ions and citrate ions are markedly active in causing colloids to give up water and prevent colloids from absorbing water. Therefore a diuresis should theoretically result from the injection of ferric ammonium citrate. That the reverse is true is explained by the fact that the iron salt promptly becomes intracellular in the convoluted tubules and there tends to block the further passage of water because the colloids in the cells are inhibited from absorbing water; if the solvent is thus inhibited from passing, so will also be the solutes, which view accounts for the fall in the excretion of water, carbonates and "phthalein" and the reduced specific gravity.

DISCUSSION

E. R. LE COUNT: I would like to ask Mr. Stieglitz whether there is any evidence of a reabsorption of iron. Some views have been advanced that some substances pass into the renal epithelium and then again back into the blood.

A. J. CARLSON: The Ludwig or mechanical theory of urine formation, in my judgment, has not been even debatable the last 15 or 25 years. At that time the accumulation of evidence for the secretion theory was complete. Here is another bit in the same direction. I should like to ask Mr. Stieglitz, in view of the fact that normally little (an infinitesimal amount) of the iron eliminated goes by way of the kidney (it is eliminated by the alimentary tract), whether he could get similar pictures in the mucosa cells of the small intestine.

A. B. LUCKHARDT: I would like to ask whether Mr. Stieglitz lowered the blood pressure so as to rule out filtration through the glomeruli; if he found the blood pressure was low, he could rule out filtration of the glomeruli and the tubules below. It is well known that if the blood pressure drops below 30 mm. of mercury all filtration of the glomeruli stops. If that has not been shown, it is possible that a good part of the urine has been filtered through the glomeruli.

E. J. STIEGLITZ: In answer to Dr. Le Count, I can say that iron was never seen in the glomerular capsules, that it probably entered the urine by the convoluted tubules. For several days after the injection of iron there was still iron in the convoluted tubules. There was never iron in the urine at that time. I cannot say whether it enters the glomeruli.

In regard to Dr. Carlson's question: Sections of the intestinal mucosa and of the spleen and liver were studied following injections of iron. The distribution of that iron following intravenous injection seems to be to the kidney, to Kupfer's cells of the liver and to the cells of the spleen, particularly in the splenic pulp. There was some iron in the mucosa, but the concentration was by no means that which one sees in the urine. This does not prove that the physiologic route of iron elimination is possibly not through the intestine. We are merely using iron as an example of a salt, not really speaking of the normal physiology of iron.

In answer to Dr. Luckhardt's question: Such an experiment was performed in which the blood pressure was low and the iron did come through into the urine, but there was a diminished quantity of urine eliminated. In the reduction of the blood pressure to such a low level as to interfere with glomerular function, it must greatly interfere with the nutrition of the kidney and thereby interfere with the function. If it interferes with glomerular function, the effects on the tubule secretion would also be marked.

STREPTOCOCCI IN CHRONIC INFECTIONS OF THE PROSTATE AND SEMINAL VESICLES

From the John McCormick Institute for Infectious Diseases, Chicago

RUSSELL D. HERROLD

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There has been much written during the last fifteen years on the clinical and bacteriologic aspects of prostatic infections, with considerable variance in the bacteriologic reports. There has been no attempt to establish a relation between the type of infecting organism and the clinical course of the infection. This phase of the problem I have been studying in a series of cases.

Young, Geraghty and Stevens found streptococci twice in 19 cases; Squier, once in 8; Culver, 6 times in 34. Friedman and others mention staphylococci, streptococci and colon bacilli as the most common invaders in the order mentioned. Fuchs, Belfield, and more recently Vedier, emphasize the frequent occurrence of *B. coli* as the causative bacterium. Fuller gives the streptococci a prominent place. Hitchens and Brown, in a series of 45 cases, isolated streptococci in 27 instances. Other bacteria found by them were staphylococci in 25 cases, non-liquifying cocci of the staphylococcus group in 34, diphtheroid bacilli in 31, gonococcus in 5, and *B. coli* in 2. They used 10% ascites agar. I found as a rule the secondary invaders in postgonorrheal prostatitis to be staphylococci, streptococci and diphtheroids. *B. coli* was found in few cases and proteus more rarely.

The expressed prostatic fluid cultivated from 109 cases was found to contain streptococci in 34%; in 15 cases streptococci persisted on two or more later examinations, one was negative with the second culture.

The greater incidence of streptococci than generally reported by others may be attributed to the use of ascites blood phosphate agar medium which is a very favorable medium for the growth of streptococcus, discrete colonies often reaching a diameter of 3-4 mm.

The number of bacteria in the anterior third of the urethra and particularly in the fossa navicularis make it necessary that great care be used in the collection of material. A solution of potassium mercuric iodide 1:5000, which is known to be highly bactericidal for the common

bacteria of the skin, was used to cleanse the glans, and the anterior inch of the urethra was swabbed with this solution, followed by sterile water or salt solution. A part of the urine was then voided, the prostate massaged, seminal vesicles stripped and the expressed fluid collected in a sterile container and several loopfuls immediately transferred to plates. The efficiency of this technic is indicated by the fact that the cultures from the fossa, as well as from normal prostates, thus obtained are invariably sterile.

TABLE 1
FINDINGS IN STREPTOCOCCUS AND NONSTREPTOCOCCUS CASES

	Streptococcus Group	Nonstreptococcus Group
With definite lesions:		
Prostate and vesicles.....	19	15
Prostate	7	9
Vesicles	3	3
Without definite lesions.....	9	11
Percentage of pus cell content:		
Less than 25 per cent.	13	21
More than 25 per cent.	25	19
Pus free:		
Number	6	18
Average in months.....	7	3½
Pus persistent at last examination:		
Number	29	17
Average in months.....	5	3

TABLE 2
RESULTS OF AGGLUTINATION TESTS

	Number of Strains
Change of blood medium:	
Hemolysis	12
Green	13
Bile, insoluble	25
Bile, soluble	0
Agglutination results with 4 monovalent antistreptococcus serums:	
Serum 1	10
Serum 2	6
Serum 3	2
Serum 4	2
Strains not agglutinated by antistreptococcus serums.....	5

A comparison was made of an equal number of streptococcus and nonstreptococcus cases taken in the order of their occurrence. As summarized in table 1, a slightly greater number in the streptococcus class gave changes which could be detected by palpation; in 6 cases of this class with involvement of both prostate and vesicles there was extreme tenderness and marked perivesicular infiltration. An equally extensive involvement was noted only twice in nonstreptococcus cases. There seems to be a definitely higher percentage of patients with pus in the streptococcus group, and the nonstreptococcus patients appear to recover in a shorter time.

Bile solubility tests were made on all strains used in the agglutination tests. None were soluble.

There were 12 hemolytic strains and 13 green producing streptococci of the 25 used in serologic classification.

A classification of 25 strains of streptococci is being attempted by serologic methods. Monovalent antistreptococcic serum has been produced with 4 strains. The most satisfactory technic so far used is the following: 16- to 24-hour growth on ordinary phosphate ascites agar slant is suspended in from $\frac{3}{4}$ to 1 cc of salt solution which gives a sufficiently heavy emulsion for distinct results; 0.25 cc of the dilution of the antistreptococcus serum tested is added to small tubes and an equal amount of suspension added. These are placed in the incubator at 53-56 C. overnight, and the results read the next morning. Several strains which gave a flocculent suspension grown on plain blood agar, after several transfers on ascites phosphate agar, gave homogeneous suspensions which were satisfactory for agglutination. Ten strains were agglutinated by serum 1, 6 by serum 2, and 2 each by serums 3 and 4; five were not agglutinated by any of the 4 serums. This work is still in progress, and further agglutination and absorption tests will be made.

DISCUSSION

ARTHUR H. CURTIS: I wish Dr. Herrold would say a few words concerning the number of colonies which he obtained from most of these cases.

D. J. DAVIS: I think these results are very interesting because infections with the hemolytic streptococcus, particularly in the genito-urinary tract, are of quite rare occurrence. I should like to ask Dr. Herrold about the occurrence of streptococci of both kinds in the normal urethra, whether these organisms occur, and in what percentages in the normal prostate and in the normal bladder.

RUSSELL D. HERROLD (closing): In answer to Dr. Curtis: At least half of the colonies were streptococci with an average perhaps of from 20 to 50 colonies per plate. Many of them had more.

Answering Dr. Davis' question: The streptococcus in the fossa of the anterior urethra, as far as I have observed in normal cases, has been more frequently of the viridans type; In the bladder and in catheterized specimens from the kidneys, streptococci are not generally supposed to be frequently found, and I have not found them in many cases. In a few cases in which I found a streptococcus it was the viridans type.

CHANGES IN THE ALKALI RESERVE, SUGAR CONCENTRATION, AND LEUKOCYTES OF THE BLOOD IN EXPERIMENTAL INFECTIONS

EDWIN F. HIRSCH

From the Pathological Laboratory of St. Luke's Hospital, Chicago

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The intravenous injection into rabbits of suspensions of typhoid, paratyphoid A and B, dysentery, colon, Friedlander, or Welch bacilli, and pneumococci, hemolytic or nonhemolytic streptococci is followed within 1 to 2 hours by a leukopenia and a diminution of the alkali reserve of the blood. The rapidity and the degree of lowering seem to depend on the pathogenicity of the bacteria used. Following the depression of the alkali reserve and the leukopenia, there is an 18 to 24 hour interval during which the leukocytes rapidly increase in number, and the alkali reserve returns or slightly exceeds the value originally determined for the blood of the rabbit. When the alkali reserve remains depressed, the leukocytosis persists but later when it returns to or slightly exceeds the normal, the number of leukocytes also becomes normal. In experiments when the bacterial infection does not subside with such simple and prompt changes, there are irregular depressions of the alkali reserve and coincident periods of leukocytosis until both remain normal, and there is no evidence by these tests of disease in the animal.

The results of many experiments of this kind have been similar. This repetition of similar results suggests that lowering the alkali reserve of the blood sufficiently or perhaps some as yet unknown factors associated with its depression are concerned with the production of generalized leukocytosis.

With the changes in the alkali reserve of the blood mentioned, there are without doubt others as yet unsuspected and of a chemical nature, since alterations in H-ion concentration are known to accompany or bring about disturbances in the composition and properties of such an intricate solution of colloids and crystalloids as blood plasma. One of these changes it is fair to suppose concerns the dextrose of the blood, and some hint of the changes in the amount of glucose of the blood is found in the report of Rhodenberg and Pohlman who consider the hyperglycemia of animals immunized against bacteria an index

of the degree of immunization. Elias in 1913 observed glycosuria and hyperglycemia in rabbits and dogs following feeding of dilute hydrochloric acid, while even earlier writers such as Pavy in 1864, Goetz in 1867, and Naunyn in 1868 observed glycosuria following the feeding or injection of phosphoric, lactic, or hydrochloric acid. Underhill, commenting on the effect of acidosis on carbohydrate metabolism, says the introduction of acid into the organism is associated with a disturbance of blood sugar content and is manifested in one direction: namely, blood sugar content is augmented. Other writers have made similar comments.

With these observations as a basis, an experimental study in rabbits was made to determine the effect on the blood sugar concentration of intravenous injections of the pathogenic bacteria previously mentioned, paralleled by estimations of the alkali reserve of the whole blood according to Van Slyke, and by determinations of the number of leukocytes. The sugar of the blood was determined by the Folin and Wu method on 2 c c samples of blood, the total amount of blood taken from the ear veins for each set of determinations being 3 or 4 c c.

The initial lowering of the alkali reserve is accompanied by a sudden and transient increase in the concentration of the sugar of the blood which in degree seems to be in proportion with the depression of the alkali reserve, and seemingly attains its maximum when the lowest level to which the alkali reserve falls is reached. It returns within 2 to 4 hours to the normal concentration even though the alkali reserve remains depressed. These variations are not observed in the blood of rabbits injected intravenously with sterile normal salt solution, or subjected only to the handling and bleeding necessary for the experiments.

Injections of acid potassium phosphate solutions depress the alkali reserve of the blood and produce a hyperglycemia similar to that caused by bacteria. The leukocyte curves in some of these experiments are similar to those produced by injections of bacteria.

Attempts to prevent by subcutaneous injections of carbonate and bicarbonate solutions the depression of the alkali reserve of the blood following injections of typhoid, colon, or Friedländer bacilli were unsuccessful.

The changes in the number of leukocytes were paralleled by determinations of the relative ratios of the various white blood cells. During the early part of the leukopenia stage the percentage of lymphocytes is

somewhat greater than that of the polymorphonuclear leukocytes. In a short time the polymorphonuclear ratio rises so that as the leukocytes increase the percentage of neutrophil polymorphonuclear leukocytes may rise to 80 or 90. Later the lymphocytes form an increasing proportion of leukocytes until finally the normal ration is again reached. When the number of leukocytes decreases rapidly with the return of the alkali reserve to normal, the polymorphonuclear leukocytes seem to disappear first leaving a high percentage of lymphocytes in the blood.

In a number of experiments with injections of acid phosphate solutions, the changes in the number and ratio of leukocytes are similar.

An increase in the concentration of sugar in the blood with acidosis is well known. The occurrence of hyperglycemia with experimental infections seem, then, to depend on a lowering of the alkalinity of the blood, and the degree of hyperglycemia on the extent to which the alkali reserve is depressed.

DISCUSSION

A. J. CARLSON: I would like to ask Dr. Hirsch what explanation he has for the initial fall of the alkali reserve from the injection of these organisms and whether a similar fall will not follow the injection of proteoses or peptones.

JOSEPH L. MILLER: How long does this increase in the alkali reserve continue? I know it continues long after the leukocytes have apparently reached normal.

J. A. CAPPS: The relationship and apparent parallelism between the leukocytosis and the rise or fall of the alkali reserve is remarkable. They seem to be about synchronous in their reactions, that is, the leukopenia and the drop in the alkali reserve take place about the same time. Was this the usual course?

EUGENE CARY: I would like to ask Dr. Hirsch whether he found that injections of glucose had any effect on the alkali reserve restoration.

EDWIN F. HIRSCH: Diminishing the alkali reserve of the blood by intravenous injections of suspensions of living bacteria is, so far as I know, not recorded in the literature. The mechanism involved is not clear to me. No experiments have been made with injections of proteoses or peptones, so I cannot speak about the reactions following the injection of such substances. When the alkali reserve of the blood reaches a higher than normal value following the injection of the bacterial suspension, its return to normal occurs usually within 4 to 6 hours. This transient increase has been noted particularly in experiments when the depression of the alkali reserve has been marked.

Curves indicating a parallelism between variations in the alkali reserve and the number of leukocytes of the blood may be repeated by plotting the results obtained in experiments with all the bacteria mentioned.

In a limited number of experiments with injections of glucose subcutaneously into rabbits the amount of glucose given did not increase the alkali reserve; in fact, it seems with the amount of sugar injected that certain abnormal changes in the metabolism of the animals took place, and the alkali reserve of the blood was diminished.

THE BACTERIOLOGY OF THE ADENOIDS

ISADORE PILOT

From the Department of Pathology and Bacteriology, University of Illinois, College of Medicine, Chicago

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The bacterial flora of the nasopharynx has frequently been investigated with reference to the detection of carriers, particularly of the meningococcus. In such examinations cultures were obtained by the assistance of the West tube or a curved wire swab. The results of the various surveys made would indicate that the nasopharynx harbors many dangerous bacteria. It has been generally assumed that these organisms flourish among the vegetations or adenoid tissue of this region. It is, however, surprising to find that no studies have been made with the aid of improved bacteriologic methods to determine the flora of these lymphoid structures.

Pilot and Davis¹ demonstrated that swab cultures of the oropharynx were inaccurate and not a true index of the actual flora in the faucial tonsils, particularly with reference to the hemolytic streptococcus which occurred in 61% of the swab cultures of the surface of the tonsils as compared with 97% from the crypts of the excised tonsils. In order to establish definitely the incidence and number of the common pathogenic bacteria in the nasopharynx and the nasopharyngeal vegetations, a bacteriologic study of the extirpated adenoids was undertaken.

METHOD

The adenoids studied were those removed at the ear, nose and throat ward of the Cook County Hospital from April to November, 1920. The patients were children from 5 to 16 years of age without fever or acute inflammations of the respiratory passages. The adenoids selected consisted of lymphoid tissue revealing varying degrees of hyperplasia. They measured from 0.5 to 1.5 cm. in all diameters, and usually presented from 3 to 6 or more folds. In many union had taken place between the free margins of the folds, leaving slits in the tissue not unlike the crypts of the tonsils. In a few instances fatty debris and cholesterol crystals were found in such depressions, but in

¹ Jour. Infect. Dis., 1919, 24, p. 386.

none was any purulent exudate grossly visible. Macerated adenoids were discarded. These adenoids approached the normal as closely as can possibly be obtained. Cultures were made from the epithelial surface and from the depths of the vegetations between the folds and from the bottoms of the cryptlike depressions. Blood-agar plates, heated blood agar for the isolation of the influenza bacillus and Loeffler's medium for the diphtheria bacillus were employed. In 25 instances the nasopharynx was swabbed through a West tube and cultivated on fresh and heated blood agar.

RESULTS

The common pathogenic organisms were identified and studied; the results are indicated in table 1.

TABLE 1
THE INCIDENCE OF PATHOGENIC BACTERIA IN THE ADENOIDS, NASOPHARYNGEAL SWABS
AND TONSILS

Organism	Number of Patients	Adenoids % Positive	Nasopharyngeal	
			Swab % Positive	Tonsils % Positive
<i>Streptococcus hemolyticus</i>	103	61	..	..
	25	..	40	..
	21	..	..	95
<i>Streptococcus viridans</i>	103	89	..	..
	21	..	90.5	81
<i>Pneumococcus</i>	103	65	..	..
Type 2	..	2	..	..
Type 3	..	10.3	..	..
Type 4	21	52.7	71.4	66.6
<i>Mathers coccus</i>	103	17	..	..
<i>Staphylococcus</i>	103	60	..	..
Gram negative cocci	103	79	..	..
<i>B. influenzae</i> (Pfeiffer)	115	40.9	..	53.9
	25	..	40	..
<i>B. diphtheriae</i>	100	12	..	12
Diphtheroids	100	30	..	17
<i>B. mucosus capsulatus</i>	103	14	..	..
<i>B. fusiformis</i>	10	20	..	..

Streptococcus Hemolyticus.—Hemolytic streptococci occurred in 61% in cultures taken from the depths between the folds and of the crypts. In 18 these organisms were quite numerous and in 3 in pure cultures. In their hemolytic properties, morphology and carbohydrate fermentation they conformed to the beta type mostly of the *Streptococcus pyogenes* group. They were bile insoluble and pathogenic for rabbits in doses of 2 c.c. and for mice in 0.5 c.c. of broth culture. The alpha type was encountered in 20%.

Streptococcus Viridans.—*Streptococcus* colonies causing methemoglobin formation on blood agar occurred in 89%. They were bile insoluble and did not ferment inulin. On the basis of carbohydrate

fermentation 30% of the strains were of the *Streptococcus mitis* group, 64% of the *Strep. salivarius* and 6% of the *Strep. fecalis*. Streptococci causing neither hemolysis nor green formation were noted in 12%; streptococcus mucosus in 3%.

Pneumococcus.—Bile soluble, inulin fermenting strains were found in 65%. Of these, on the basis of agglutination with specific serums, 85% were type 4, 13% type 3, and 2% type 2. With the exception of 2 strains, the type 3 were culturally like *Pneumococcus mucosus*.

Mathers Coccus.—Large, moist, often flat, green producing colonies variable in bile solubility and inulin fermentation conforming to the streptococcus described by Mathers² in the past influenza epidemic were found in 17%.

Bacillus Influenzae (Pfeiffer).—On heated blood-agar mediums influenza bacilli were recovered in 40.9%, often in large numbers. They were identified as gram-negative, pleomorphic bacilli failing to grow on infusion agar, and showing the characteristic property of symbiosis.

Bacillus Diphtheriae.—From Loeffler's medium granular types morphologically identical with the Klebs-Loeffler bacillus were isolated in 12%, often predominating on this medium, and in pure culture in 2 instances. Two strains were toxin-producing killing guinea-pigs in doses of 1 c.c. of broth culture, while the antitoxin controls survived. The remainder were relatively avirulent. In this connection it should be noted that the patients whose adenoids gave positive cultures did not have diphtheria.

Diphtheroids.—Organisms resembling closely in their cultural characteristics the diphtheria bacillus, but morphologically different in that they did not show metachromatic granules, occurred in 30%. They were further differentiated by their inability to ferment the ordinary sugars.

Other Organisms.—Staphylococci were noted in 60%, and most of them were of the albus and only a few the aureus type. Gram-negative diplococci were encountered in 79%, appearing chiefly as *Micrococcus catarrhalis*, *Micrococcus pharyngis siccus* and a few resembling the meningococcus. A study is now being made for their further differen-

² Tunncliffe, R.: Jour. Infect. Dis., 1920, 26, p. 405.

tiation. The *Bacillus mucosus capsulatus*, growing as large mucoid colonies, was found in 14%. Anaerobic cultures were made of 10 adenoids and the *B. fusiformis* occurred in 2 (20%).

CULTURES OF THE NASOPHARYNGEAL SWABS OF THE SAME PERSONS

Nasopharyngeal swab cultures were taken from 25 persons before operation. Few hemolytic streptococci were found in 10 persons (40%) as compared with those found in the depths of the adenoids in 15 persons (60%). Influenza bacilli occurred once in the adenoids of a person in this series (44.4%) when it was not recovered from the swab (40%). Pneumococci and streptococcus viridans appeared in the same percentages. It was notable, however, that all of these organisms were decidedly more numerous in the depths between the folds and in the cryptlike depressions than on the epithelial surface and the nasopharyngeal swab, demonstrating the tendency of these organisms, especially the hemolytic streptococcus, to flourish in the recesses of the nasopharynx.

CULTURES OF THE CRYPTS OF THE TONSILS FROM THE SAME PERSONS

The extirpated tonsils of 21 persons were cultivated and revealed hemolytic streptococci in 20 (95%), frequently in predominating numbers, while the adenoids of 15 (71.4%) of these patients contained these organisms in less numbers. The pneumococci were present in 66.6% and the *Streptococcus viridans* in 81% as compared with 71.4% and 90.5%, respectively, in the adenoids. In those instances in which the pneumococci and green streptococci were absent in the tonsils and present in the adenoids the tonsillar crypts harbored hemolytic streptococci in pure culture. The tonsils of 115 patients were found to have influenza bacilli in 53.9%, whereas the adenoids of the same persons gave positive results in 40.9%. Diphtheria bacilli occurred in 12% of the tonsils and adenoids of 100 children, appearing more often in predominating numbers in the tonsils.

THE INCIDENCE OF HEMOLYTIC STREPTOCOCCI, PNEUMOCOCCI AND *B. INFLUENZAE* IN THE NASOPHARYNX OF TONSILLEC- TOMIZED AND NONTONSILLECTOMIZED CHILDREN

Normal children from 5 to 15 years of age, inmates of an orphan asylum, were swabbed in the nasopharynx. After the bacteriologic

work was completed, they were divided in two groups, those who had had their tonsils and adenoids removed from 2 months to 5 years previously and those who did not have either excised. A few children having remnants of tonsils were classified as nontonsillectomized. In 48 with tonsils hemolytic streptococci were recovered in 27 (56.3%) and in 27 without tonsils in 11 (40.8%); influenza bacilli occurred in 17 (39.3%) of 43 persons with tonsils and in 8 of 29 (26.5%) persons without tonsils. J. Meyer found pneumococci in about the same percentage (32.5%) in both groups. It is noteworthy that all of these organisms when present were decidedly fewer in tonsillectomized than in the nontonsillectomized persons.

While the removal of the tonsils and adenoids reduces the incidence and numbers of bacteria in the throat and nasopharynx it is quite evident that it does not cause their disappearance, and that the other lymphatic structure of the oro- and nasopharynx continue to furnish foci for these organisms.

The Flora of the Nasopharynx of Normal Persons.—Every culture taken from the nasopharynx and adenoids showed various organisms. Regardless of the size of the adenoids, or whether or not the vegetations were to be considered normal or markedly hypertrophied, microorganisms, particularly the streptococci, pneumococci and *B. influenzae* were present, occasionally one predominating over the other, seldom, however, in pure culture. Usually several different organisms were found in the same person in a considerable percentage. It would therefore seem that for children, at least, the organisms commonly encountered should be regarded as part of the normal flora of the nasopharynx, just as we regard certain bacteria as part of the normal flora of the mouth or intestine.

Significance with Special Reference to the Carrier Problem.—On the basis of these results, it is quite apparent that many healthy persons harbor pathogenic bacteria in the nasopharynx, organisms which do not differ from the strains isolated from various pathologic processes of the human body. Can all such persons be termed carriers in the sense that they are sources from which others may become infected? Under exceptional circumstances transmission of hemolytic streptococci from one person to another directly by droplet infection or indirectly through milk, for example, occurs as illustrated in the epidemic streptococcal complications following measles and the milk epi-

demics of streptococcus sore throat. In such instances an epidemic strain of enhanced virulence exists in the throats of the affected persons and those who come in contact with them. Under ordinary circumstances, however, these organisms apparently lie dormant in the tonsils and nasopharynx without harm to the healthy person or to the healthy contact. The carrier state may possibly be limited to persons harboring epidemic strains and to the convalescents and contacts giving positive cultures of the organisms responsible for cases of diphtheria, meningococcic meningitis, and pneumonias due to type 1 and 2 pneumococci. The adenoids, like the tonsils, should be considered as foci where such dangerous organisms may persist.

SIGNIFICANCE OF THE BACTERIA OF THE ADENOIDS AS SECONDARY INVADERS

In the healthy person the micro-organisms apparently exist without doing harm. When, however, the resistance is lowered, either locally by acute inflammations of the respiratory tract as in the exanthemata, pneumonia and influenza or generally by an acute or chronic toxemia or a chronic debilitating disease, these organisms may become a great source of danger. Hemolytic streptococci are commonly secondary invaders in measles, scarlet fever, pneumonia and other primary infections. The pneumococcus, particularly types 3 and 4 and the influenza bacillus are the predominating secondary invaders in influenza. In chronic conditions, such as tuberculosis, nephritis, malignancy, leukemia and other diseases, the streptococcus and pneumococcus are the chief causes of the terminal infection. It seems unlikely that the organisms causing secondary infection in such a variety of conditions are all introduced from without. They may sometimes be acquired from other persons, but it is more logical to assume that many patients succumb to the secondary invasion of the organisms of their own oro- and nasopharynx. It should also be pointed out that from the same sources the complications of otitis media and inflammations of the accessory sinuses of the respiratory tract undoubtedly originate.

SUMMARY

Cultures were taken from the excised adenoids to determine more definitely the flora of the nasopharynx. Pathogenic bacteria were found in every specimen. Of the more important organisms, hemolytic strep-

tococci occurred in 61%, pneumococci in 65%, *B. influenzae* in 40.9%, *B. diphtheriae* in 12%. Other streptococci, diphtheroids, staphylococci, gram-negative cocci, *B. mucosus capsulatus* and *B. fusiformis* were encountered.

The depths between the folds and bottoms of the crypt-like structures of the adenoids harbored hemolytic streptococci, pneumococci and *B. influenzae* in larger numbers than the epithelial surface or the nasopharyngeal swabs.

A series of nasopharyngeal swabs of normal children revealed the same organisms in a considerable percentage; it is therefore evident that these organisms are a part of the normal flora of the nasopharynx.

The removal of tonsils and adenoids reduces the bacteria of the nasopharynx, but considerable numbers still persist.

The adenoids, like the tonsils, are to be considered common foci where dangerous bacteria flourish and sources from which secondary infection may arise in the course of primary acute respiratory diseases and of chronic debilitating diseases.

EXPERIMENTAL LESIONS OF THE HYPOPHYSIAL REGION AND POLYURIA

McMICKEN HANCHETT

From the Department of Anatomy, University of Chicago

This work was begun for the purpose of determining experimentally the effect of intravenous injections of extract of the pituitary gland on the so-called polyuria of hypophysial origin. Before it had proceeded far, attention was attracted to certain striking variations from the generally accepted ideas concerning the production of polyuria of this type, and it seemed wise to investigate the means of producing it.

Dogs were used in all the experiments. Ether was used as the anesthetic and during the operation was administered by the intra-tracheal method. The gland was exposed by the buccal (transpharyngeal) route, first described accurately and used successfully by Aschner. In each case the normal urine excretion for 24 hours was measured as a preoperative control.

Synopsis of work:

1. Stimulation of the anterior and posterior lobes of the hypophysis: (a) varying degrees of heat; (1) heated rod; (2) paraffin; (b) trauma-pinching and pulling with tissue forceps; (c) cone-shaped plug of beeswax pushed into opening in bone; (d) induced current—electrical.

2. Herniation of gland through dural opening.

3. Traction on base of brain with as little trauma to the gland as possible.

4. Effect of pituitary extract, epinephrin and thyroid extract on polyuria.

Stimulation of the Anterior and Posterior Lobes of the Hypophysis with Heated Rod.—In this group 10 animals were used. After exposing the hypophysis, the gland was stimulated by traumatizing it with a metal rod of varying temperatures. The local effect, observed post-mortem, varied from a moderate hyperemia of the anterior and posterior lobes to complete destruction of the gland. In only one instance was a polyuria of any considerable extent observed.

For 9 animals of this group the average 24-hour urine measured 210 c c and 204 c c for the 2 days immediately preceding the operation, and 220 c c, 214 c c, 224 c c, 286 c c, 250 c c, 180 c c, 260 c c and 200 c c for the successive days after operation.

In dog 2 there was a marked polyuria. The daily preoperative urinary excretion was 200 c c. The stimulation consisted in trauma with a rod heated to "blackhot" point, that is, the point at which the rod appears black after cherry red has faded. The rod was 3 mm. in diameter and was simply brought in contact with the structures at the bottom of the opening after the dura had been incised. At this stage in our work our landmarks were not as thoroughly impressed on us as they later were, and we were not able to locate the hypophysis definitely. During the first 24 hours practically no urine was voided. In the second 24 hours the quantity was 650 c c, and during the third 24 hours the amount increased to 1,500 c c. At this time the dog appeared to be very sick; scarcely able to stand. It was killed at the end of the third 24 hours. At postmortem examination it was found that our opening through the sphenoid bone was so far posterior that the hypophysis had not been exposed and that our stimulation had been applied to the base of the brain posterior to the hypophysis, the region of the corpora mamillaria.

Stimulation with Heated Paraffin.—In dogs 14, 37 and 39, paraffin heated to 70 degrees, 110 degrees and 130 degrees C. was poured into the cavity in the sphenoid bone without otherwise disturbing the gland. In dog 37 the dura was not incised. In no instance was there any change in the amount of urine excreted.

Mechanical Trauma Pinching and Pulling with Tissue Forceps.—In dogs 10, 11 and 21 the gland was traumatized by pinching and pulling on the anterior and posterior lobes with tissue forceps. On the 2 days preceding the operation the average urinary output was 150 c c in 24 hours. During the 24-hour period immediately after operation the average rose to 297 c c, after which it gradually fell until it reached 180 c c at the end of the fourth 24-hour period after operation.

Cone-Shaped Plug of Beeswax Pushed Into Opening in Sphenoid.—In dog 71a a cone-shaped plug of beeswax, approximately 1 cm. in diameter at the base and 1 cm. long, was forced into the opening in the sphenoid against the hypophysis. The gland was tipped slightly forward so that the plug impinged on both the anterior and posterior lobes. The preoperative excretion had been averaging 250 c c to 300 c c daily. The postoperative excretion was slightly less, being 150 c c to 250 c c daily. After 10 days of observation, the dog was apparently in normal physical condition and was used for other experimental work.

Induced Electrical Current.—The gland was stimulated by means of an induced current in dogs 58, 63, 66, 69a and 70a. In each instance there was an increase in the daily amount of urine. This was most marked in dog 63. During the 2 days preceding the operation the urine excreted in 24 hours measured 300 c.c. Following electrical stimulation the amount increased to 1,400 c.c. in the first 24 hours, 3,800 c.c. in the second 24 hours and 4,200 c.c. during the third 24 hours. This polyuria lasted for 6 days, but as the urinary output was modified by other experimental work for which this animal was used, the remaining period will be discussed in detail later.

Herniation of the Gland Through the Dural Opening.—In dog 15 the sphenoid bone was much wider than is usual, and the surrounding venous sinuses were correspondingly formed in a larger circle. This made wider incision of the dura possible. When this step in the operation was performed, the gland herniated through the opening, forced through by a gush of cerebrospinal fluid. The degree of protrusion of the gland and the amount of spinal fluid were greatly in excess of anything previously noted. No manipulation was necessary to bring the gland well into view. A small portion of the anterior lobe was removed and the operation stopped. The dog was in excellent condition at the close of the operation. The urinary output during the 3 days previous to operation was 160 c.c. per 24 hours. This increased to 2,360 c.c. during the first 24 hours and to 3,680 c.c. during the second 24 hours following operation. It then fell to 2,140 c.c. in the third 24 hours. The dog was in excellent condition but was killed at this time in order that the tissue might be studied during active polyuria.

Dog 28 was operated on in the usual manner, and in this instance also the gland was forced through the dural opening by cerebral pressure. This herniation was not so marked as in the former case. Slight traction was made on the stalk, but an effort was made to avoid injury to the gland. The urine voided during the 2 days preceding operation measured 90 c.c. and 100 c.c. During the first postoperative 24 hours 900 c.c. were passed. The quantity decreased to 200 c.c. during the second 24 hours. At this time this animal was in such bad condition that it was released from its cage. It died the following day. Post-mortem examination showed no evidence of meningitis. The cause of death was bronchopneumonia. On the basis of these two observations, a group of 20 dogs was operated.

Traction on Base of Brain with as Little Injury to the Gland as Possible.—In these animals an effort was made to avoid trauma to the gland itself, while making traction on the stalk and its attachment to the floor of the third ventricle. The traction was made by introducing behind the gland a pair of dental cotton-holding forceps, the points of which extended forward beneath the pars nervosa. The stalk was grasped as gently as possible and the traction made through it on its attachment.

The complete result of this entire group may be briefly summarized as follows: average preoperative excretion in 24 hours, 150 c c; post-operative excretion per 24 hours, first—955 c c, second—960 c c, third—865 c c, fourth—700 c c, fifth—700 c c, sixth—500 c c, and seventh—190 c c.

The most marked polyuria of this group occurred in dog 55. The output increased from 200 c c on the days preceding operation to 4,000 c c during the second 24 hours after operation. This dog was allowed to live 6 days and was in good condition when killed. Postmortem examination showed a hemorrhage into the third ventricle. The hypophysis showed no gross changes other than the plastic exudate filling the defect in the sphenoid and covering the anterior lobe of the gland.

It will be noted that the entire number of the dogs in this group were not allowed to survive the full length of 7 days. It had been noted in our work, as in that of others, that a polyuria induced by stimulation in the region of the hypophysis was almost invariably a transitory condition, and its duration and the typical curve had been frequently described. Therefore, after the highest point in excretion had been reached, or at least such a point as could be definitely regarded as a polyuria, many animals were used for supplementary experiments. Some were killed to secure tissue at the height of urinary excretion for cytological study. Others were used to observe the effect of pituitrin and epinephrin on polyuria produced by stimulation in the region of the hypophysis.

Effect of Pituitary Extract.—Dogs 55, 56, 59a, 63 and 64 were each given M XV of pituitary extract (P. D.) in the femoral vein. In every instance there was a rapid drop in the curve of urinary excretion in the 24 hours following the injection. In 4 cases there was a secondary rise in the curve of the excretory rate followed by a more gradual decline.

Effect of Epinephrin.—Epinephrin was used in animals 67, 68, 69, 69a and 70. Doses of MV, M VIII and M X were injected into the femoral vein during active polyuria with no apparent change in the usual excretory curve.

In examining these results and the general problem of the etiology of polyuria of this type, one is at once brought face to face with the two schools of opinion:

1. Those who contend that the hypophysis, especially the pars intermedia, pars nervosa and infundibulum, is the important factor in the regulation of urinary excretion.

2. Those who believe that polyuria when associated with pituitary disease is, to borrow an expressive phrase, a "neighborhood symptom."

The inaccessibility of the gland accounts in a large measure for this difference of opinion. It is difficult even by microscopic examination to determine just what injury was done to the gland and to the neighboring base of the brain at the time of operation.

Every method of approach has its disadvantages. The two most generally used are the transtemporal (Paulesco) and the transsphenoidal (Aschner). The certainty of a definite amount of infection, the danger of hemorrhage and the inaccurate estimation of stimulation or trauma inflicted to the gland and adjacent structures are some of the objections to the method used in this work. On the other hand, we feel sure that the variable, unmeasured and unestimated traction on the attachment of the infundibulum to the floor of the third ventricle, when the gland is dislocated upward and laterally in order to expose the gland by the bitemporal (transtemporal) method, may be a very important factor in the production of the rather variable results obtained relative to polyuria.

As to the objections to the manner of approach used in this work, it may be said only one animal showed any evidence of infection other than the slight plastic exudate over the exposed portion of the anterior lobe. In this case a cotton pack was inserted to fill the opening in the sphenoid. In all others the opening was left wide open and thus maintained free drainage into the mouth. By care we were able to avoid hemorrhage.

While it is impossible to regulate accurately the degree and extent of the injury inflicted to the gland and its neighboring structures, we found no urinary increase of any consequence in any of the animals in which either the anterior or posterior lobes individually, or the entire gland, were stimulated by non-diffusible means, i.e., heat or mechanical trauma.

Stimulation of the hypophysis with an induced current produced polyuria. However, as an electrical stimulus may be transmitted over a considerable distance, it cannot be said that this trauma is limited to the gland itself, or that the resulting urinary increase is of hypophysial origin.

By traction on the stalk with an effort to avoid trauma to the gland itself, we were able to produce a polyuria regularly. We were able also to regulate roughly the degree of this increase, moderate or extreme, by modifying the amount of trauma (traction) exerted. Other animals operated, in which the same procedure was followed except for traction on the stalk, showed no or only slight polyuria.

It may also be said that in those experiments in which the hypophysis was mechanically stimulated, the injury to the gland was greater than that inflicted in the process of making traction on the stalk. In the case of the former group, the average daily pre-operative output of 150 cc was increased to 297 cc in the first twenty-four hours and then gradually decreased, reaching normal in four days. In the latter series the average daily pre-operative excretion of 150 cc was increased to 955 cc in the first twenty-four hours. It remained high and had not quite descended to the pre-operative level by the end of the seventh day.

The 3 outstanding experiments to which we would like to call special attention are those performed on animals 2, 15 and 55. In dog 2, the opening in the sphenoid was made so far posterior that the hypophysis was not exposed, and the stimulation (cauterization) was applied to the region of the corpora mamillaria. In dog 15, due to peculiar anatomic arrangements, the gland came through the dural incision with considerable force, followed by a larger amount of cerebrospinal fluid than had been usually observed. Except for these variations there was nothing done which had on previous occasions produced more than a negligible increase in the urinary excretion. In dog 55 there was found at postmortem examination a hemorrhage into the third ventricle. This animal was operated in the series in which traction was made on the stalk and its attachment to the base of the brain. The associated polyuria was the most marked in this group.

In these 3 animals we see: first, a conspicuous increase in the urinary output, and second, the presence of an additional etiologic factor. In dogs 2 and 55 there is gross evidence of injury to the base of the brain. In animal 15 the force with which the gland herniated through the dural opening may be considered to have produced trauma of the same sort but not appreciable microscopically. This is in accord with the results and conclusions of Camus and Roussy, which were published in 1914, but which did not come to our attention until after the completion of this work.

In the 6 dogs given intravenous injections of pituitary (P.D.) there was a definite transitory antidiuretic effect.

Epinephrin in 5 dogs and freshly prepared thyroid extract in 2 dogs produced no notable change in the quantitative urine in polyurias of this type.

DISCUSSION

JOSEPH L. MILLER: This view is very interesting. I believe it was Kahler who injected into the anterior lobe silver nitrate and found that he could produce in animals a polyuria that lasted for several days. He also stated that drugs containing silver nitrate would do exactly the same thing in man—they would give a polyuria of several days' duration.

S. A. MATTHEWS: In regard to the question of polyuria induced by injury to the base of the brain, there seem to be two opinions; one, that it is due to injury in the region of the third ventricle, and the other that it is due to injury of the pituitary body.

Quite frequently, following the operation for extirpation of the pituitary body by the sphenoidal route in dogs, there is a polyuria of high degree, lasting from 24 to 72 hours. Out of about 100 operations on the pituitary gland (dogs) I have induced 3 cases of polyuria of a permanent character, lasting for from 6 to 8 weeks. The polyuria was of high degree; 5 to 6 liters (6 to 7 kilo dogs) in 24 hours and without sugar. The polyuria was accompanied by an intense polydipsia, both of which could be reduced to almost

normal by the administration of pituitary extract. In all of these animals the pituitary body was partially removed and some injury was inflicted in the region of the attachment of the infundibulum to the floor of the third ventricle.

As injuries in this region are frequently followed by polyuria (sometimes with glycosuria) without injury to the pituitary body, most observers consider the polyuria due to brain injury and not to injury of the pituitary gland.

A. J. CARLSON: This communication brings to mind the fact that the correct observations of great men may at times lead us far astray by faulty reasoning. Schaefer years ago showed that intravenous injection of pituitary extract in dogs under anesthesia acted as a temporary diuretic. If this was a physiologic action the next step followed logically. Injury to the hypophysis may liberate too much of this renal hormone and we have the polyuria of diabetes insipidus. This view is still held by many clinicians. The theory is logical and based on a perfectly correct observation that in animals under anesthesia the intravenous injection of pituitary extract causes a temporary diuresis; but if the administration of pituitary extract is made without an anesthetic and one takes a 24-hour urine specimen, there is no diuresis. It is clear to us now that Schaefer's experiment did not permit the physiologic and clinical inferences drawn from it, and hence the complete "about face" in the rôle ascribed to the hypophysis in polyuria.

McMICKEN HANCHETT (closing): I do not think I have anything to say except that this work was done at the suggestion of Dr. Dean Lewis on a fund which was furnished by Madam McCormick.

I am sorry that the time is so limited that we cannot enter into the discussion of the literature a little more fully. I agree with Camus and Roussy, who say that when it is impossible on gross pathologic grounds to explain any clinical phenomenon, there is a tendency to attribute it to some disturbance of the ductless glands.



NATHAN S. DAVIS, II
1858-1920

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Nathan Smith Davis, A.M., M.D., was born in Chicago, Sept. 5, 1858, being the younger of two sons of the distinguished physician and publicist, Nathan Smith Davis, M.D., LL.D., the founder of the American Medical Association and its early president, also the founder of its famous *Journal of the American Medical Association* and its first editor. The elder Davis was also one of the founders of the Chicago Medical College—now called Northwestern University Medical School.

The two sons of this famous American scientist followed in his footsteps and became physicians. The older, Dr. Frank Davis died shortly after entering practice, the younger, the subject of this biography, lived to carry out many of the ideals of his famous family and had a distinguished career in American medicine.

The writer knew Nathan S. Davis II as a boy, as a young man in his university and medical college course, and was afterward associated with him in college organization and general scientific societies—such organizations as the Illinois Microscopical Society and the Chicago Academy of Sciences. We spent much time together in amateur botanical and geological expeditions.

We also traveled and studied together in European universities. Dr. Davis was something of a naturalist. He was of a studious and book-loving temperament, but not the less a man of wide personal influence. He joined national and international scientific bodies. He traveled much to take part in the work of these associations, and his personal acquaintance was very wide among literary and scientific men. He was genial and magnetic rather than aggressive in his relations with people, and few who knew him well ever forgot his kindly, polished manners, his charm in speaking in public or private or the air of culture and a sort of old-school distinction that shone in his intercourse with others.

He resembled his famous father in features, having the broad, high forehead and deep orbits which made a face full of power and intellect. He was a handsomer man, of larger frame, than his father but less forceful—dynamic. Instead of the fiery eloquence and commanding leadership of the older Davis, he had rather the qualities of the pure

scientist, the research man, the nature lover, the post-naturalist—he was of the type of a Thoreau or a John Burroughs.

He shone in personal work among his colleagues. His fine, tall, handsome presence, his love of humanity and his mastery of the graces of intercourse made him greatly beloved by his students. He was none the less a good organizer and executive in university and public affairs.

While a student he won honors for scholarship. He lived in Evanston while attending the University there, and later entered the Medical School in Chicago. He stood number one in his class and at graduation was awarded the annual prize for highest scholarship with the A.M. and M.D. degrees in 1883.

His medical education was rounded by a postgraduate course at Vienna, where Dr. Frank Billings, Dr. George Isham, Dr. Elbert Wing, Dr. Frank Johnson and the writer, all young Chicago graduates, were more or less working as a group. Dr. Davis, with only American-taught French and German, rapidly perfected himself as a linguist, having a natural aptitude for languages, and before he left Europe had been accepted as assistant by Professor Arnold of Heidelberg, who usually declined to take non-German speaking men into his pathologic laboratory.

Continuing his career in Chicago, Dr. Davis was an able teacher in pathology at Northwestern University Medical School, holding the position of assistant professor in 1884. He was later appointed to the chair of practice of medicine. For a time he acted as secretary of the faculty and later succeeded Dr. Frank Johnson as dean of the medical department, holding that position for many years. He was also attending physician of Mercy and of Wesley hospitals, during these years, giving clinical lectures.

Dr. Davis gave considerable time and energy to national scientific bodies, being for many years first vice-president of the United States Pharmacopoeia Convention and a member of the Pan-American Medical Congress. In the Ninth International Medical Congress he was councilor of the Section on Pathology. At the same time he was active as a Fellow of the American Climatological Association, the American Tuberculosis Society, the Chicago Tuberculosis Institute and was one of the founders of the Chicago Institute of Medicine. He was also a Fellow of the American Medical Association and for a time was one of a group who gave valuable aid in the establishment of the *Journal*

of the *American Medical Association*, of which the Senior Davis was the founder and editor.

Dr. Davis was a trustee in many institutions; the Chicago Academy of Science, (chairman of the board); Northwestern University and the Young Men's Christian Association (vice-president). He was a member of numerous clubs and fraternities.

As a writer Dr. Davis' name was familiar in the scientific and medical journals of America. He was also the author of several books: "A Treatise of General Practice," made up of his lectures, and one on "Consumption—How to Live with It," "Diet in Health and Disease" and numerous monographs.

He had resided in California for nearly two years in an effort to regain declining health. For several years he had suffered from glandular enlargement which at times invaded the mediastinal spaces and which was believed to be lymphosarcoma. Although temporarily relieved by radiotherapy, recurrence finally became general, and he died Dec. 21, 1920, aged 62, at his home in Los Angeles.

E. WYLLYS ANDREWS

ANNOUNCEMENTS

The following have been elected fellows of the Institute:

Edmund Andrews
Wm. F. Peterson
Leon Bloch
S. A. Mathews

The next Pasteur Lecture will be given by Dr. Theobald Smith of Princeton, N. J., in October, 1921.

The following Fellows have been placed on the nonresident list:

Henry F. Helmholtz, removed to Rochester, Minn.
Richard S. Dewey, removed to California.
Fred Gaarde, removed to Rochester, Minn.
Philip Schuyler Doane, removed to California.

On April 29 a dinner was given by the Institute in honor of Sir William Herringham, chairman of the committee on medical education of the British Grants Committee and Vice Chancellor of the University of London, and Sir Walter Fletcher, secretary of the British Medical Research Council and Senior Demonstrator of Physiology, Cambridge University.

On June 20 a dinner was given by the Institute in honor of Dr. Carlos Chagas, Director Oswaldo Cruz Institute, Rio Janeiro, and Director of Public Health, Brazil. Dr. Chagas gave an illustrated lecture on American trypanosomiasis, a synopsis of which will appear in the next issue of the *Proceedings*. In responding to the introduction of the president of the Institute, Dr. Chagas said:

It is difficult for me to express as I wish my gratitude for the high honor that you have shown me in your country. You have received with the greatest kindness a modest Brazilian research worker whose scientific work is but enough to give him a modest name in his own country, and when compared with the great scientific work performed by the intelligent scientists of this country is as unknown. Fortunately, I understand your attitude, and in it I find once more the evidences for a high spirit of international cordiality; in it I recognize the superiority of a great people, always eager to stimulate and to promote scientific development in the farthest places of the world. From afar off in my own dear country we follow always wondering the great development of your scientific progress and applaud without limit memorable deeds that you add every day to your memorable history. In the field of science and especially in the scientific branches of medicine you reached very early the highest point of perfection. I have followed very closely your medical organization and in that I admire every day the power of your will and the efficiency of your culture. You have advanced very rapidly in your scientific evolution and you did it, gentlemen, dominated by that valuable sentiment of human solidarity that compels you to diffuse the benefits of your greatness to the other people of the world; that quickens you with the highest motives for promoting the happiness of life in all the world. Happy indeed is that country that is able to be a beautiful example of civilization and at the same time a great leader in altruism and moral greatness. Unfortunately, my dear friends, I do not speak your language with the perfection necessary to express to you exactly the gratitude I feel. It does not matter, however, because the language of the heart is always the same everywhere, and it is through the heart that I thank you very much.

STORAGE

